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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/705, 16/28, C12N 5/10, G01N 33/68	A1	(11) International Publication Number: WO 99/29847 (43) International Publication Date: 17 June 1999 (17.06.99)
(21) International Application Number: PCT/US98/23161 (22) International Filing Date: 30 October 1998 (30.10.98) (30) Priority Data: 08/985,809 5 December 1997 (05.12.97) US (71) Applicant (for all designated States except US): LOYOLA UNIVERSITY OF CHICAGO [US/US]; 2160 South First Avenue, Maywood, IL 60153 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): PEREZ-REYES, Edward [US/US]; 320 South Birchwood Drive, Naperville, IL 60540 (US). CRIBBS, Leanne, L. [US/US]; 1737 North Natoma, Chicago, IL 60707 (US). (74) Agents: HEFNER, M., Daniel et al.; Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, 180 North Stetson, Chicago, IL 60601-6780 (US).		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME (57) Abstract <p>The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.</p>		

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T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

This invention was made with Government support under Grant Number HL58728 awarded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. The United States Government may have certain rights in this invention.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to cloned T-type calcium channels.

BACKGROUND OF THE INVENTION

Biological membranes are themselves generally impermeable to ionic species. Thus, ions enter cells through regulated pores formed from membrane-associated proteins. Most of these regulated pores are voltage-dependent and are thus able to transduce changes in the transmembrane potential into ion flux. Voltage-gated ion channels form a "superfamily" of related proteins (cf. Jan et al., *Nature*, 345, 672 (1990)). Peculiar to this genus is a high degree of conservation in molecular structure. Generally, voltage-gated channels are membrane bound glycosylated proteins formed of many subunits. Large α subunits form a pore in the membrane that is selective for a given ionic species. Each α subunit contains four domains (I, II, III, and IV). Each channel domain has six putative transmembrane helical segments (S_1 - S_6). In general, the segments within each domain are similar but not identical. Aside from overall structural conservation, certain charged residues within the domains are highly conserved among voltage-gated ion channels (Jan et al., *supra*; Stühmer et al., *Nature*, 339, 597-603 (1989)).

Differences in charged residues between groups of voltage-gated ion channels confer properties unique to each subgroup, such as ion selectivity. For example, most voltage gated ion channels are selective for either sodium, potassium or calcium. Known calcium channels require a ring of negative charge provided by glutamate residues found at similar locations in each of the domains (Yang et al., *Nature*, 366, 158-61 (1993)).

Voltage-gated channels are often classified on the basis of their electrophysiology. The resting membrane potential of most animal cells is between about -70 mV and -80 mV. When the membrane becomes depolarized (moved towards 0 mV), various membrane channels become activated (they are said to

“open”). Thus, one basis for classifying membrane channels is the membrane potential necessary to activate (or “gate”) them (voltage dependency). For example, “T-type” calcium channels are activated at a lower voltage than L- or N-type channels (Nowycky et al., *Nature*, 316, 440-43 (1985)). Other physiological properties are the activation kinetics, inactivation kinetics, tail current (deactivation kinetics), and single channel conductance. Thus, in comparison to other calcium currents, T-type calcium current is characteristically short (Chen et al., *J. Gen. Physiol.*, 96, 603-30 (1990)), and it exhibits characteristically slow activation kinetics near threshold, fast inactivation kinetics, and slow tail current (Randall et al., *Neuropharmacol.*, 63, 879-93 (1997); Carbone et al., *Nature*, 310, 501-02 (1984); Nilius et al., *Nature*, 316, 443-46 (1985)).

Calcium currents have been implicated in many neurological and muscular functions. For example, T-type calcium current is associated with cardiac pacemaker activity, pain transmission in the central nervous system, and in other physiological functions. Defects in T-type calcium current have been implicated in cardiac arrhythmia, hypertension, and epilepsy. Given their potential clinical value, the pharmacological properties of calcium channels have been the subject of extensive study. Most such studies have involved L-type channels because, unlike T-type channels, L-type calcium channels are readily purified from cell extracts. For example, L-type calcium channels have been purified using dihydropyridine drugs (e.g., nifedipine) which can bind with sufficiently high affinity to serve as a ligand for purifying L-type calcium channels. Such purified and cloned L-type calcium channels have been used to develop assays for drugs affecting L-type calcium channels (see, e.g., U.S. Patents 5,429,921 and 5,386,025).

While many electrophysiological characteristics of T-type calcium currents are known, the lack of isolated T-type channels has stalled research into the pharmacology and biophysics underlying the T-type calcium current, at least in comparison with other calcium channels. Indeed, while it is generally assumed that voltage-sensitive ion channels are responsible for the current, no such channel protein, nor any nucleic acid encoding such a protein, has been isolated. In view of the foregoing problems, there exists a need for an isolated T-type calcium channel and a nucleic acid encoding a T-type calcium channel.

BRIEF SUMMARY OF THE INVENTION

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or

substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

The present invention is useful for exploring the electrophysiology and pharmacology of the T-type calcium current. Such knowledge can lead to the development of drugs for potentiating or attenuating T-type calcium channels. Thus, the present invention provides an assay for identifying potential drugs affecting T-type calcium channels by exposing cells expressing a T-type calcium channel to a putative drug and then measuring the calcium flux in response to a change in membrane potential. The identification of drugs affecting T-type calcium channels will facilitate even greater understanding of the biophysics of these proteins. Furthermore, some such drugs could have potential clinical applications.

The invention can best be understood with reference to the accompanying drawings and in the following detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1E compare the complete amino acid sequences of three types of T-type calcium channels ($\alpha 1G$ (or $Ca_vT.1$), $\alpha 1H$ (or $Ca_vT.2$), and $\alpha 1I$ (or $Ca_vT.3$)), indicating conserved functional domains.

Figures 2A-2D are graphic representations of the current-voltage relationships of three cloned T-type calcium channels (Figures 2A, 2B, and 2C) and a cloned R-type calcium channel (Figure 2D).

Figure 3A is a graphic representation of the average current-voltage curve for cloned T-type calcium channels ($\alpha 1G$, triangles, $\alpha 1H$, inverted triangles, $\alpha 1I$, circles), and a cloned R-type calcium channel (filled squares). Figure 3B compares the normalized conductance of a cloned T-type calcium channel at three different concentrations of $BaCl_2$.

Figure 4 depicts average kinetics of the tail current as a function of repolarization potential for $\alpha 1G$ (triangles), $\alpha 1H$ (inverted triangles), $\alpha 1I$ (circles), and a cloned R-type calcium channel (filled squares).

Figures 5A and 5B graphically present data concerning the use of a cloned T-type calcium channel to detect drugs affecting the channel. Figure 6A depicts the effect of 100 μM on current-voltage relationships with a single dosage of mibefradil. Figure 6B illustrates the effect on T-type channel conductance of various doses of mibefradil.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α

subunit. The nucleic acid can be of any type, and it can include other elements aside from a sequence encoding a T-type calcium channel domain or domains. For example, where the nucleic acid comprises RNA, it can also include regulatory sequences suitable to permit translation of the RNA. Thus, an RNA nucleic acid of the present invention preferably has at least one ribosome entry site, and preferably has a polyadenosine tail for stabilizing the RNA in the cellular environment.

Similarly, DNA nucleic acids of the present invention can have regulatory elements for promoting the transcription of sequence encoding the T-type calcium channel into an RNA such as that described above. For example, a DNA nucleic acid of the present invention can have a promoter and/or an enhancer sequence. While the nucleic acid can be any type of nucleic acid, the nucleic acid preferably comprises a cDNA. A cDNA nucleic acid is preferred over other nucleic acids to permit the nucleic acid to be readily cloned, sequenced, and expressed in a wide variety of cells.

The choice of promoter and/or an enhancer will largely depend on the milieu in which the nucleic acid is to be expressed. Thus, for expression in bacterial cells, the regulatory elements are bacterial promoters. Similarly, for expression in mammalian cells, the regulatory elements are able to effect expression in mammalian cells. While many such regulatory elements are known in the art, examples include prokaryotic promoters and viral promoters (e.g., retroviral ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit β -globin regulatory elements), constitutively active promoters (e.g., the β -actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters (e.g., those active in epidermal tissue, dermal tissue, tissue of the digestive organs (e.g., cells of the esophagus, stomach, intestines, colon, etc., or their related glands), smooth muscles, such as vascular smooth muscles, cardiac muscles, skeletal muscles, lung tissue, hepatocytes, lymphocytes, endothelial cells, sclerocytes, kidney cells, glandular cells (e.g., those in the thymus, ovaries, testicles, pancreas, adrenals, pituitary, etc.), tumor cells, cells in connective tissue, cells in the central nervous system (e.g., neurons, neuralgia, etc.), cells in the peripheral nervous system, and other cells of interest).

The isolated or substantially purified nucleic acid of the present invention encodes all or part of a T-type calcium channel α subunit. As used herein, a "calcium channel" includes a protein structure for facilitating the flux of calcium ions across a biological membrane into which the calcium channel is inserted. As used herein, a "T-type channel" is a type of voltage-gated ion channel that facilitates the flux of ions

when the membrane potential of a biological membrane into which it is inserted experiences a slight depolarization. Thus, a T-type calcium channel can begin to gate from about -60 mV to about -30 mV (i.e., about -45 mV to about -35 mV) in about 10 mM Ba^{2+} . Additionally, T-type channels of the present invention exhibit a slow
5 deactivation (tail current) following depolarization. Thus, a T-type calcium channel can exhibit a tail current that decays exponentially with a tau value from about 1 ms to about 10 ms (e.g., from about 4 ms to about 7 ms, such as about 6 ms) following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a Ba^{2+} concentration of from about 10 mM to about 40 mM. Another
10 defining characteristic of T-type calcium channels is that they exhibit small single channel conductance. Thus, for example, a T-type channel exhibits a single channel conductance of from about 4 pS to about 12 pS (e.g., from about 6 pS to about 10 pS), and typically from about 7 pS to about 9 pS in a solution with a Ba^{2+} concentration of about 0.1 M.

15 The isolated or substantially purified nucleic acid of the present invention encodes all or part of any T-type calcium channel having at least one of the aforementioned electrophysiological properties when properly assembled within a cellular membrane. The general structure of calcium channels is summarized above and is otherwise known in the art. Thus, for example, the nucleic acid can encode one
20 of the four functional domains mentioned above. As used herein, a domain of a T-type calcium channel is any protein structure able to associate with three other domains to form a tetrameric body functioning as a T-type calcium channel. While the native T-type calcium channel structure includes all four domains in a single polypeptide (indicated in Figures 1A-1E), a domain can exist as a polypeptide species
25 separate from those containing the other domains. Such separate domains are able to associate within the plasma membrane to form a functional channel. Alternatively, where a plurality of domains are linked within a common polypeptide, the linkage can deviate substantially from the native linkage. Thus, for example, the domains can be linked by polypeptide sequences other than those sequences linking the domains in the
30 native protein (e.g., non-native polyglutamate linkages). Indeed, the domains themselves can include non-native linkages between membrane-spanning elements within the domains. Aside from these modifications, the nucleic acid can encode a chimeric calcium channel domain (or an entire channel) comprising a portion of a T-type calcium channel and a portion derived from another calcium channel (or other
35 channel) protein. For example, the chimera can include portions of domains from T-type channels responsible for low voltage gating and portions of domains from other calcium channels responsible for slow inactivation. Such a protein exhibiting T-type gating but longer inactivation kinetics would facilitate pharmacological research.

As mentioned, nucleic acids of the present invention can encode an entire T-type channel (i.e., a T-type channel protein comprising four functional domains). It has been discovered that at least three genes encoding T-type calcium channels exist in humans and rats (i.e., $\alpha 1G$ (or $Ca_vT.1$), $\alpha 1H$ (or $Ca_vT.2$), and $\alpha 1I$ (or $Ca_vT.3$)), and alternate splicing of these isoforms exist. Examples of the amino acid sequences of full-length T-type channels, and the sequences of suitable coding nucleic acids are set forth at SEQ ID NOs:1-8 ($\alpha 1G$ sequences), SEQ IS NOs:9-10 ($\alpha 1H$ sequences), and SEQ ID NOs: 11-12 ($\alpha 1I$ sequences). However, the invention is not limited to these exemplary sequences. Indeed, as mentioned, an amino acid sequence of a T-type calcium channel can vary from those listed, and it is within the state of the art to change a nucleotide sequence encoding a T-type channel to introduce mutations into the protein. Indeed, for conducting electrophysiological assays, it may be desirable to introduce mutations into such a protein. For example, mutations comprising insertions or deletions can be introduced on either the amino- or carboxy-terminus of the protein, or such mutations can be intrasequence insertions or deletions. Where the electrophysiological properties of the calcium channel are to be conserved, such mutations preferably are in regions other than the membrane spanning domains. However, in some applications (e.g., to decrease inactivation kinetics), the changes can be within the membrane-spanning regions. Moreover, as mentioned above, the sequence can form a protein having only one functional domain of a T-type calcium channel. Additionally, the sequence can also form a chimeric protein or domain, such as those described above.

Aside from insertions and deletion mutations of native T-type calcium channel sequences, a T-type calcium channel can include substitutions of amino acid residues, e.g., for those indicated in SEQ ID NOs:1-12. Preferably, and especially where such a substitution is within a membrane spanning region, the substitution is conservative. Thus, within membrane spanning domains, positively-charged residues (H, K, and R) preferably are only substituted with positively-charged residues; negatively-charged residues (D and E) preferably are only substituted with negatively-charged residues; neutral polar residues (C, G, N, Q, S, T, and Y) preferably are only substituted with neutral polar residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are only substituted with neutral non-polar residues. Preferably, any amino-acid substitution within the membrane-spanning regions does not alter this conservation. Most preferably, any substitution, deletion, or insertion does not alter the IVS4 domain. In each of the exemplary T-type calcium channel α subunit sequences, the putative IVS4 region comprises SEQ ID NO:13. Given the strong sequence conservation among families of voltage-gated ion channels, it is likely that this sequence or a derivative sequence, will be present in T-type channels. Thus, the

present invention provides any T-type calcium channel (or a nucleic acid encoding such a T-type calcium channel) comprising SEQ ID NO:13 or a sequence derived from SEQ ID NO:13 having conservative amino acid substitutions, as described above.

5 The nucleic acid of the present invention encoding all or a part of a T-type calcium channel can be isolated via any suitable method. For example, prior to the present invention, one of skill in the art could design a probe based on the sequence of known, non-T-type, calcium channels and use such probe to screen a genetic library. If such a screen were to identify a putative calcium channel, the researcher could then
10 attempt to clone the entire nucleic acid to characterize it. Similarly, prior to the present invention, to isolate a nucleic acid encoding a T-type calcium channel, one of skill in the art could consult publicly available databases containing DNA sequences (e.g., Genbank) to locate nucleic or amino acid sequences representing a portion of a T-type calcium channel protein or nucleic acid. However, such databases contain no
15 sequence for a full-length T-type calcium channel or identify any sequence as a T-type channel. Such methods assume that T-type calcium channels share sufficient sequence identity with known calcium channel nucleic acids to cross-hybridize, an assumption not supported by any published report. Moreover, prior to the present invention, no partial sequence in such databases was identified as corresponding to a
20 T-type calcium channel. Thus, prior to the present invention, the presence of partial sequences in the public DNA databases could facilitate the isolation of T-type calcium channels only with the exercise of a considerable degree of speculation on the part of the researcher.

By providing several sequences pertaining to T-type calcium channels and a
25 comparison presenting conserved regions and domains, the present invention greatly facilitates the isolation of other nucleic acids encoding T-type calcium channels (or derivatives thereof) with much less experimentation. Thus, while any of the methods discussed above can be employed to isolate other members of this genus, preferably, a nucleic acid encoding a T-type calcium channel is isolated by probing a genetic library
30 using a probe that hybridizes to a DNA encoding a peptide sequence contained in (or similar to) a known T-type calcium channel (e.g., SEQ ID NOs:1-12). To facilitate the isolation of a T-type calcium channel, the present invention provides an isolated polynucleotide hybridizing to a portion of the nucleic acid of the present invention encoding a T-type calcium channel (or a portion thereof). Thus, for example, the
35 present invention includes an isolated polynucleotide hybridizing to SEQ ID NO:1-12. The isolated polynucleotide can hybridize to all or any portion of the sequence encoding the T-type calcium channel.

To isolate such a polynucleotide, any portion of a sequence encoding a T-type calcium channel can be employed as a probe to screen a genetic library, and such screening can be accomplished by standard techniques known in the art. While the probe can hybridize to any portion of such a DNA, preferably the probe is designed to hybridize to a DNA encoding a polypeptide sequence that is highly conserved among T-type calcium channels but is less conserved between the genus of T-type calcium channels and other proteins. Such peptide sequences are readily apparent from the sequence comparison set forth in Figures 1A-1E. Generally, the specificity of hybridization in a genetic screen varies depending on the length of the probe and the stringency (e.g., temperature, salt and detergent concentration, etc.) of hybridization. Stringency of hybridization is broadly classified as "high," "moderate," or "low," and the parameters of these terms are well recognized in the art (see, e.g., Sambrook et al., "Molecular Cloning, a Laboratory Manual," Cold Spring Harbor Press, 1989). The isolated polynucleotide hybridizing to a portion of the nucleic acid encoding a T-type calcium channel can hybridize under any desired stringency conditions. However, for identifying other T-type channels, preferably, the hybridization occurs under moderate stringency, and most preferably under high stringency.

Of course, the isolated or substantially purified polynucleotide can itself be employed as a probe to screen a library as described to isolate a second nucleic acid. In such a screen, one of the polynucleotides will be complementary to a portion of the sequence encoding the T-type calcium channel, and the other isolated nucleic acid will be "sense." Preferably, one of the two isolated polynucleotides (the "sense" strand) itself encodes a T-type calcium channel, or at least one domain thereof. Such a sequence can be cloned to be operably linked to suitable regulatory elements, as described, to produce a T-type calcium channel. Thus, aside from using the nucleic acid of the present invention to produce a T-type calcium channel, the nucleic acids of the present invention are also useful for isolating other sequences encoding T-type calcium channels, or derivatives thereof.

However isolated, the isolated or substantially purified nucleic acid of the present invention is useful, in part, for producing all or a portion of a T-type calcium channel. Thus, the nucleic acid can be introduced into a suitable milieu for driving its expression. Because T-type channels are transmembrane proteins, preferably such a milieu is a living cell. However, it should be understood that the nucleic acid can also be expressed *in vitro* under conditions, such as those known in the art, suitable for *in vitro* transcription and translation. However produced, the present invention includes any protein, such as a recombinant protein or an isolated or substantially purified protein, including all or a portion of a T-type calcium channel or a protein derived from a T-type calcium channel.

For expression in a living cell, the nucleic acid must be introduced into the cell. As nucleic acids are generally introduced into cells as part of genetic vectors, the present invention provides a vector having a T-type calcium channel nucleic acid of the type described above. Any type of vector suitable for introducing the nucleic acid into a host cell is within the context of the present invention. Examples of such vectors include naked DNA and RNA vectors (such as oligonucleotides, plasmids, capped cRNA, etc.), viral vectors such as adeno-associated viral vectors (Berns et al., *Annals of the New York Academy of Sciences*, 772, 95-104 (1995)), adenoviral vectors (Bain et al., *Gene Therapy*, 1, S68 (1994)), herpesvirus vectors (Fink et al., *Ann. Rev. Neurosci.*, 19, 265-87 (1996)), packaged amplicons (Federoff et al., *Proc. Nat. Acad. Sci. USA*, 89, 1636-40 (1992)), papilloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors, vaccinia virus vectors, and other vectors. Once a given type of vector is selected, its genome must be manipulated for use as a background vector, after which it must be engineered to incorporate exogenous polynucleotides. Such manipulations are known in the art.

The vectors of the present invention are useful for introducing a nucleic acid encoding all or a portion of a T-type calcium channel into a host cell. Thus, the present invention provides a cell into which the vector of the present invention has been introduced. The host cell can be any cell suitable for expressing the nucleic acid (e.g., bacteria, insect cells, mammalian cells, etc.). The host cell can thus be *in vitro* or *in vivo*. Preferably the cells do not exhibit native T-type calcium current. A preferred cell type is HEK-293 cells because they contain genetic elements that facilitate the expression of transgenes from a variety of expression vectors. For facilitating electrophysiological recordings, oocytes (e.g., *Xenopus* oocytes) are preferred, as they are large and readily handled.

The vector can be introduced into the cell in any manner suitable for the cell type and vector employed. In one embodiment, the vector can be used to prepare an RNA transcript *in vitro* (e.g., a capped cRNA) which is then introduced into the host cell by standard methods (such as injection). Such techniques are preferred when the host cells do not actively transcribe DNA (such as oocytes). In other embodiments, a DNA vector is introduced into the cell such that it is transcribed within the cell. For example, the vector can be introduced into the cell such that it forms an extrachromosomal segment of genetic material in the cell, as is the case with many types of viral vectors. Alternatively, the vector can introduce the nucleic acid into the chromosomal DNA of the host cell.

Preferably, a cell into which the nucleic acid is introduced is also able to express the nucleic acid to produce the α subunit protein. The expression of the nucleic acid can be detected by probing the cell for the presence of T-type calcium

channel mRNA, such as via Northern hybridization analysis, in situ hybridization, etc. More preferably, however, the cell is able to express the nucleic acid to produce the protein including all or a portion of a T-type calcium channel. In such cells, expression of the nucleic acid is confirmed by detecting the protein, for example, by
5 probing cellular extracts with an antibody recognizing the protein (e.g., on a Western blot, etc.).

In the membrane of the cell producing the protein, the expressed protein contributes to the formation of a functional calcium channel. Where the protein encodes an entire α subunit, the full protein will possess some or all of the
10 electrophysiological properties of T-type calcium channels described above. Where the protein encodes less than an entire channel α subunit (e.g., a domain), the protein will aggregate with other constituent domains in the membrane to form a functional channel. Thus, the presence of the protein can be detected by assaying the cell for T-type calcium channel activity. Indeed, assaying for channel activity serves to
15 determine whether a nucleic acid encoding a putative calcium channel, in fact, encodes a species of T-type channel (as opposed to a member of another genus of calcium channels). For example, when large cells (e.g., oocytes) are used as the host cells, the electrophysiological properties of the channel can be investigated. Thus, the membrane activity of whole cells expressing the nucleic acid can be measured
20 directly, such as via patch clamp techniques using a voltage clamp electrode and a current electrode (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). Alternatively, the activity of single channels can be measured, such as with a standard depolarizing bath and pipette solutions (Lacerda et al., *Biophys. J.*, 66, 183-43 (1994)). However measured, the properties of cells into which the putative nucleic
25 acid is introduced are compared to the channel conductance, voltage dependency, activation kinetics, inactivation kinetics, or tail current known for T-type channels and discussed above. A measure of current density (e.g., pA/pF) can also be used to assess the level of gene expression in the cells, normalizing for cellular volume.

While, in accordance with the present invention, an isolated cell into which the
30 T-type calcium channel nucleic acid has been introduced (and preferably stably expressing the nucleic acid to produce the protein) can be prepared, preferably, such transfection protocols result in a population consisting essentially of such transfected cells. For standardizing the results of many experiments, it is even more desirable to employ an established cell line consisting essentially of such cells. Preferably, for use
35 in high throughput assays, cell lines stably expressing a T-type calcium channel exhibit a current density of at least about 40 pA/pF (e.g., at least about 45 pA/pF), such as about 50 pA/pF or even 55 pA/pF or higher. Preferably, a cell line in accordance with the present invention is able to propagate the nucleic acid through

several passages (e.g., for at least 10 passages), and, preferably, the nucleic acid is stably integrated into the chromosomes of such cells. Thus, the cell line can propagate the nucleic acid for at least 20 passages, and more preferably significantly more than 20 passages (e.g., at least about 25 passages, or even more).

5 Regardless of the cell system, the ability to express a T-type calcium channel nucleic acid within host cells to produce an active channel permits the channel to be further studied. In this regard, the present invention provides a method of identifying a drug which affects T-type calcium channels. The method involves first expressing a T-type calcium channel in a cell to produce an active channel, as herein described.

10 The cell expressing the channel is then exposed to a solution containing a putative drug for interfering with the channel. Thereafter, the presence or absence of calcium flux in response to a change in membrane potential is assayed. Any such assay can be employed within the context of the present invention, (e.g., using labile dyes, radioisotopes (e.g., ^{45}Ca), recording electrophysiological changes in the membrane,
15 etc.). A quick method of assaying for calcium flux is first to introduce a calcium-sensitive labile dye into the cells. For example, the dye can be one such as those that fluoresce or change color in the presence of calcium, many of which are known to those of skill in the art (e.g., Indo-1). Thereafter, the cells are exposed to a depolarizing solution containing high (e.g., about 50 mM) potassium concentration
20 and a drug, and the reaction of the labile dye is compared to control cells. Using a labile dye affords the ability to assay many putative drugs quickly in a high throughput assay for putative drugs affecting T-type channels. For example, the initial screening can be carried out in 96 well plates. Moreover, dose-response data can be readily generated by exposing the cells to several concentrations of the same putative
25 drug.

Once a putative drug is detected, its effect on the electrophysiology of the cell (e.g., single channel conductance, voltage dependency, activation kinetics, inactivation kinetics, and tail current of the cells) can be investigated in detail.

Generally, the effect of the putative drug on T-type calcium currents is assessed by
30 measuring the various electrophysiological parameters in the presence of various concentrations of the drugs and comparing the data to untreated (or sham-treated) control cells. Cells preferably are maintained in a continuous perfusion chamber during such experiments to facilitate changing solutions. The inventive method of identifying a drug which affects T-type calcium channels can employ any nucleic acid
35 encoding a T-type calcium channel (or derivative thereof), such as those nucleic acids described herein. In fact, as several isoforms of T-type channel exist, the assay method can be repeated using nucleic acids encoding different isoforms to identify

drugs that preferentially target a given isoform, or drugs which affect more than one isoform of T-type calcium channels.

Aside from affording an *in vitro* assay for detecting potential therapeutic or investigative drugs targeting T-type calcium channels, the method of expressing the T-type calcium channel nucleic acid can also be used *in vivo*. For example, as mentioned, several neurological and muscular diseases or disorders have implicated mutations affecting native nucleic acids encoding T-type calcium channels. The present invention, thus, provides a method of treating a disease or disorder associated with a deficiency in a native T-type calcium channel nucleic acid. The method involves introducing a vector having the T-type calcium channel nucleic acid into cells of a host in which native expression of the nucleic acid is deficient. Thus, for example, for treating cardiomyopathy associated with deficiencies in T-type calcium channels, the vector is introduced into myocardial cells. Similarly, for treating forms of epilepsy associated with deficiencies in T-type calcium channels, the vector is introduced into neurons (e.g., thalamic neurons). Within the target cells, the nucleic acid within the vector is expressed to produce active T-type calcium channel. By similar methods, an nucleic acid having a sequence antisense to a sequence encoding a T-type calcium channel (or a portion thereof) can be expressed within a cell. The presence of an antisense sequence can down-regulate the expression of native T-type calcium channel genes by hybridizing to T-type channel mRNA within the cell. Thus, the present invention is useful to treating disorders associated with over-expression of T-type calcium channels.

T-type channel proteins (such as whole T-type calcium channels, domains of such channels, chimeras including portions of T-type calcium channels, etc.) can be employed to generate antibodies (e.g., immunoglobulins) to T-type calcium channels. Thus, the present invention provides an isolated and substantially purified antibody molecule recognizing an epitope on a T-type calcium channel. Such antibodies can be monoclonal antibodies or polyclonal antisera. Antibodies recognizing T-type calcium channels can be used to purify the channels from cell extracts or other solutions by standard methodologies (e.g., immunoprecipitation). Moreover, depending on the location of the epitopes for the antibodies on the T-type calcium channel, the antibodies can be used to affect the channel proteins present on the surface of cells. Thus, antibodies directed to T-type calcium channels are potential reagents for studying the channels as well as for therapy.

Such antibodies can be produced by any suitable method, many of which are well known in the art. Thus, for example, the antibodies can comprise polyclonal antisera obtained from inoculated animals. Alternatively, the antibody molecules can be monoclonal antibodies obtained from a cell line (e.g., a hybridoma cell line). Thus,

the present invention provides a cell which produces such antibodies. Such a cell can be *in vitro* or *in vivo*; however, where the cell is *in vitro*, preferably it is within an established cell line consisting essentially of such cells.

Several examples are presented below to illustrate the invention. Taken
5 together, the examples demonstrate the cloning of twelve novel proteins and their characterization as T-type calcium channel α subunits. These examples are included here for purely illustrative purposes; as such, they are not to be construed so as to limit the scope of any aspect of the invention.

Many procedures employed in the following examples are techniques routinely
10 performed by one of ordinary skill in the art (see generally Sambrook et al., *Molecular Cloning. A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)) and are not discussed in detail. However, some reagents and methods deserve specific description. Thus, for example, *in vitro* translation and expression were conducted as described previously (Schneider et al., *Receptors and Channels*, 2,
15 255-70 (1995)). *Xenopus laevis* oocytes were prepared as described previously (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). To express proteins, 10 or 30 ng of capped cRNA was injected into the oocytes in a volume of 50 nl. For single channel recording, oocytes were injected with 100 ng capped cRNA and incubated for one week prior to assay.

20 Cells were voltage clamped using a two-microelectrode voltage clamp amplifier as described (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). The standard bath solution contained the following: 40 mM Ba(OH)₂, 50 mM NaOH, 1 mM KOH, 0.1 mM EDTA, and 5 mM HEPES, adjusted to pH 7.4 with methanesulfonate. The osmolality of the 2 mM Ba²⁺ and 10 mM Ba²⁺ solutions was
25 balanced by increasing the NaOH concentration as described (Lory et al., *J. Physiol. (London)*, 429, 95-112 (1990)). Voltage and current electrodes (1.5-1.8 M tip resistance) were filled with 3 M KCl. Except as noted, data were acquired at 4 kHz using the pCLAMP system, and filtered at 1 kHz. Data were analyzed using pCLAMP software. Boltzman fits and linear regression were calculated using Prism.

30 EXAMPLE 1

This example demonstrates the cloning and characterization of putative T-type calcium channels.

35 A search of the Genbank library was conducted to identify clones identified as having some degree of homology to known calcium channel sequences. The search identified an expressed sequence tagged (EST) partial sequence in a human brain clone (H06096), which was used as a probe to screen a λ gt10 cDNA library prepared

from rat brain. Successive screening of the cDNA library identified five overlapping clones which were aligned to construct an entire cDNA sequence, termed $\alpha 1G$.

The $\alpha 1G$ cDNA was cloned into the pSP72TM vector and sequenced by standard computer-assisted sequencing. Using the $\alpha 1G$ cDNA, the amino acid
5 sequence of the $\alpha 1G$ protein was deduced and compared to the sequences of other known calcium channel α subunits. By similar methods, homologous human (H19230 and R19524) and mouse (AA286626) EST clones were also identified and partially sequenced, and alternately spliced variants were identified. The deduced
10 cDNA and amino acid sequences for eight full-length $\alpha 1G$ T-type channels are set forth, respectively, as SEQ ID NOs:1-8.

A second T-type calcium channel, termed $\alpha 1H$, was isolated by screening a human heart cDNA library with a fragment of the $\alpha 1G$ sequence. An alternately spliced isoform was also identified. The full-length cDNA and amino acid sequences for these $\alpha 1H$ T-type channels are set forth, respectively, as SEQ ID NOs:9 and 10.

15 A third T-type calcium channel, termed $\alpha 1I$, was isolated by screening a rat brain cDNA library at low stringency using a fragment of the rat $\alpha 1G$ gene. Fifty plaques were identified, many of which were not detected in a second screening. A third screening with a fragment from $\alpha 1H$ identified two clones. Subsequent screening, and the use of the GenBank database, led to the identification of the full
20 length rat and human cDNA and amino acid sequences, set forth at SEQ ID NOs: 11 and 12, respectively.

The $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ amino acid sequences were compared to each other and a known calcium channel ($\alpha 1E$) to investigate the conservation of protein
25 structure and function. The comparison indicates that the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ amino acid sequences within the putative membrane-spanning domains are about 90 % identical to each other, while the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ sequences are only roughly 40 % identical to the $\alpha 1E$ clone.

Figures 1A-1E indicate this conservation between the proteins. The conservation of charged residues, particularly in the S4 domains, is consistent with the
30 role of the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins as ion channels. However, two of the glutamates associated with ion specificity in other calcium channels have been replaced with aspartate, suggesting altered ion selectivity. Strikingly, $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ display only low homology to sequences linking the membrane-spanning regions within each domain, and even less homology between the intracellular loops linking
35 domains. Notably, neither $\alpha 1G$, $\alpha 1H$, nor $\alpha 1I$ possesses sequences known to bind β subunits or Ca^{2+} ions.

EXAMPLE 2

This example demonstrates the production of cell lines stably expressing the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins.

HEK-293 cells were transfected with either the rat $\alpha 1G$ cDNA (SEQ ID NO:1), the human $\alpha 1H$ cDNA (SEQ ID NO:9), or the rat $\alpha 1I$ cDNA (SEQ ID NO:11). As a control, cells were also transfected with human $\alpha 1E$ plus human $\beta 3$ (Schneider et al., *Receptors Channels*, 2, 255-70 (1994); Murakami et al., *Eur. J. Biochem.*, 236, 138-43 (1996)). The DNA constructs included a neomycin resistance gene conferring resistance to G418. The cells were cultured under standard conditions using medium containing G418 to select for stable transformants.

Surviving clones were expanded and assayed for electrophysiological activity to determine the presence of channels within the membrane. Whole-cell currents were recorded from ruptured patches using an Axopatch 200A amplifier, Digidata 1200 A/D converter, and pCLAMP 6.0 software. Data were digitized at 2 kHz and filtered at 1 kHz or off-line. All experiments were performed at room temperature. Pipettes were made out of TW-150-6 capillary tubing (World Precision Instruments, Inc., Sarasota, FL), using a Model P-97 Flaming-Brown pipette puller (Sutter Instrument Co., Novato, CA). The internal pipette solution contained the following: 55 mM CsCl, 75 mM CsSO₄, 10 mM MgCl₂, 0.1 mM EGTA, 10 mM HEPES, pH adjusted to 7.2 with CsOH. The external Tyrodes solution was the following: 140 mM NaCl, 6 mM KCl, 2 mM CaCl₂, 10 mM glucose, 5 mM HEPES, pH 7.4. The recording solution contained the following: 10 mM BaCl₂ solution (or 2 mM CaCl₂), 140 mM tetraethylammonium (TEA) chloride, 5 mM CsCl, 1 mM MgCl₂, 5 mM glucose, and 10 mM HEPES, pH adjusted to 7.4 with TEA-OH. Under these solution conditions the pipette resistance was typically 1.5-2.5 M Ω . Cell capacitance was measured by integrating the charging current during a 10 mV hyperpolarizing pulse (holding potential -80 mV).

Using these recording techniques, values for pA/pF were obtained for each cell line, which is a measure of current density normalizing for cell size. One clone (#N2) expressed the rat $\alpha 1G$ protein and has a current density of 42 pA/pF. Another clone (#13), expressed the human $\alpha 1H$ protein and exhibited a current density of 53 pA/pF. Three clones (#11, #19, and #25) expressed the rat $\alpha 1I$ protein and exhibited current densities of 40 pA/pF, 45 pA/pF, and 55 pA/pF, respectively.

EXAMPLE 3

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type current-voltage relationships.

Current traces were elicited by depolarizing voltage clamp pulses of the membranes of cells. The $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins were produced in *Xenopus laevis* oocytes by linearizing the DNA vectors containing the coding sequences, and transcribing the coding sequences *in vitro* by standard methods. Oocytes were then injected with the capped RNA.

Figures 2A-2E depict data obtained from these experiments using cells injected with $\alpha 1G$ (Figure 2A), $\alpha 1H$ (Figure 2B), and $\alpha 1I$ (Figure 2C) and $\alpha 1E$ (Figure 2D). These data indicate that cells expressing $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ exhibit T-type calcium current, while oocytes expressing $\alpha 1E$ as well as uninjected oocytes (Figure 6A) do not.

Current voltage curves were developed using cells injected with $\alpha 1G$, $\alpha 1H$, $\alpha 1I$, and $\alpha 1E$. Figures 3A depicts such data generated in a 10 mM Ba^{2+} test solution. These data were transformed into conductance and fit with a Boltzman equation to determine the midpoint of activation ($V_{0.5}$). Gating potentials for $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ (-38 ± 1 mV $n=8$, -44 mV ± 1 mV, $n=10$, and -31 mV ± 1 mV, $n=6$, respectively) were in accordance with the gating potential measured for the HEK-293 cells (-41 ± 1 mV, $n=10$), while $\alpha 1E$ required significantly more positive potentials to open (-2.6 mV $\pm .4$ mV, $n=3$).

To compare the characteristics with published values (Huguenard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)), the $\alpha 1G$ current was recorded at varying concentrations of Ba^{2+} . As indicated in Figure 3B, in solutions containing 2 mM Ba^{2+} , $V_{0.5}$ was -46.5 mV, and the slope factor (k) was 6.6 ($n=7$). However, when the Ba^{2+} concentration was 40 mM, $V_{0.5}$ was recorded at -21 mV, presumably due to the results of barium on surface charge screening (see, e.g., Wilson et al., *J. Membrane Biol.*, 72, 117-30 (1983)). Similar values were recorded for $\alpha 1H$ and $\alpha 1I$.

These results indicate that $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ are low-voltage activated calcium channels (i.e., from about -60 mV to about -30 mV in 10 mM Ba^{2+}).

EXAMPLE 4

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type tail current.

Tail current was measured at -90 mV after first opening the channels with a voltage step to -10 mV. The voltage-dependence of tail current in cells expressing $\alpha 1G$ (oocytes) $\alpha 1H$ (HEK 293 cells), and $\alpha 1I$ (HEK 293 cells) was measured at varying test potentials. As a control, tail current was also measured from a high voltage activated channel $\alpha 1E$, which Raw data from recordings data were fit with a single exponential and plotted as a function of depolarization potential (Figure 4).

These results demonstrate that the tail currents for the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ calcium channels are voltage-dependent, consistent with known T-type calcium tail currents. Additionally, these data demonstrate that the tail current for each of the cloned channels is between about 1 ms and about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

EXAMPLE 5

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type single channel conductance.

Measurement of single channel conductance is complicated by the low probability of channel opening at negative potentials when the driving force is large. Thus, single channel conductance was measured similarly for measurements of tail currents to enhance channel opening at negative potentials. Single channels were measured with standard depolarizing bath and pipette (115 mM BaCl_2 , 1 mM EGTA, and 10 mM HEPES, pH 7.4) solutions (Lacerda et al., *Biophys. J.*, 66, 1833-43 (1994)). Data were analyzed with TRANSIT (VanDongan, *Biophys. J.*, 70, 1303-15 (1996)). Single channel amplitudes were measured by averaging the values obtained from Gaussian fits to all-points histograms of traces with openings, selected openings, or amplitude histograms of idealized openings. It has been reported that some oocytes contain a native 9 pS channel. These endogenous channels can be distinguished by their 2-fold larger current amplitudes at the potentials tested (e.g., -20 mV, $i = 0.8$ for endogenous channels as opposed to 0.4 pA for $\alpha 1G$). However, such endogenous channels were not detected either at the whole cell or single channel level in the oocytes tested.

Current through the main open state of each open channel was measured at each potential and plotted against each test potential. Single channel currents for several patches were then averaged and plotted as a function of test potential, wherein the slope of the plot indicated the single channel conductance. The average slope conductance of the $\alpha 1G$ channel was measured at 7.5 ± 1.5 pS, which corresponds with the reported values for T-type calcium channels (Hugenard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)). Similar results were also obtained with both $\alpha 1H$ (10.8 ± 1.4 pS). Data collected from recordings of the $\alpha 1I$ channels indicate that they open to two distinct amplitudes. The conductance for the small amplitude $\alpha 1I$ openings was measured at 3.9 ± 0.5 pS, while that for the large $\alpha 1I$ openings was measured at 11.4 ± 0.5 pS).

These results indicate that the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins exhibit T-type single-channel conductance (e.g., from about 4 to about 12 pS).

EXAMPLE 6

This example demonstrates that a cloned T-type calcium channel can be used for identifying a drug which affects T-type calcium channels.

5 HEK-293 cells were subjected to treatment as indicated above in Example 3, except that an experimental group of cells were exposed to a solution containing 1 μ M mibefradil, a known inhibitor of T-type calcium current. As depicted in Figure 5A, the presence of mibefradil almost completely abolished T-type current in cells
10 expressing $\alpha 1G$. Cells expressing either $\alpha 1G$ or $\alpha 1H$ were similarly treated using various concentrations of mibefradil to determine a dose-response relationship. These results, depicted in Figure 5B, demonstrate that about 50% inhibition was achieved at a mibefradil concentration of 1 μ M.

15 All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred
embodiments, it will be obvious to those of ordinary skill in the art that variations of
the preferred embodiments may be used and that it is intended that the invention may
be practiced otherwise than as specifically described herein. Accordingly, this
20 invention includes all modifications encompassed within the spirit and scope of the
invention as defined by the following claims.

What is claimed is:

1. A isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α subunit.

5 2. The nucleic acid of claim 1, wherein said protein comprises an entire T-type calcium channel α subunit.

3. The nucleic acid of claim 2, wherein said protein comprises SEQ ID NO:13.

10 4. The nucleic acid of any of claims 1-3, wherein said calcium channel begins to gate from about -60 mV to about -30 mV in 2 mM Ba^{2+} .

5. The nucleic acid of any of claims 1-4, wherein said calcium channel exhibits a tail current of from about 1 ms to about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

15 6. The nucleic acid of any of claims 1-5, wherein said calcium channel exhibits a single channel conductance of from about 4 pS to about 11 pS in a solution with a barium ion concentration of about 100 mM.

7. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of any of claims 1-6.

20 8. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of claim 7.

9. The nucleic acid of claim 8 comprising a sequence encoding at least one domain of a T-type calcium channel α subunit.

10. A vector comprising the nucleic acid of any of claims 1-9.

25 11. A cell into which the vector of claim 10 has been introduced.

12. The cell of claim 11, which expresses said nucleic acid to produce said protein.

13. The cell of claim 11 or 12, which stably expresses said nucleic acid to produce said protein.

30 14. A population of cells consisting essentially of cells according to any of claims 11-13.

15. An established cell line consisting essentially of cells according to any of claims 11-13.

35 16. A method of identifying a drug which affects T-type calcium channels, said method comprising expressing a T-type calcium channel in a cell, exposing said cell to a putative drug, and measuring the calcium flux through the membrane of said cell in response to a change in membrane potential.

17. The method of claim 16, wherein said calcium flux is assayed by using a calcium-sensitive labile dye within said cell.

18. The method of claim 16, wherein said calcium flux is assayed by measuring the electrophysiological properties of said cell.

5 19. The method of claim 16, wherein said calcium channel comprises SEQ ID NO:13.

20. An isolated or substantially purified immunoglobulin recognizing an epitope on a T-type calcium channel protein.

21. A cell *in vitro* which produces the immunoglobulin of claim 20.

10 22. An established cell line consisting essentially of cells according to claim 21.

hCavT1a MDEEDGAGAEESGQPR-----SFMRLDLSGAGRPGPGSAEKDPGSADSEAEGLPYPALAPVVFVLSQDSRPSRWCRLRTVCNPW
 rCavT1a MDEEDGAGAEESGQPR-----SFTQNDLSGAGRQPGPGSTEKDPGSADSEAEGLPYPALAPVVFVLSQDSRPSRWCRLRTVCNPW
 hCavT2a MTEGARAADDEVVRVPLGRRPWPVGVGPGEPGRGAGTRGGGFGELGVSPSESPAERCAELGADEEQRPYPALAAATVFFCLGQTTRPSRWCRLRLVCNPW
 hCavT3 MAESASPPSSAAA-----PAAEPGVTTTEQPGPRSPSPSPGLEEPLDGADPHVPHDLPAPIAFAFFCLRQTTSRPNWCIMKVCNPW
 rCavT3 MADSNLPPSSAAAP-----APEPG--ITEQPGPRSPSPSPSPGLEEPLDGNPDVPHDLPAPVAFCLRQTTSRPNWCIMKVCNPW

IS1

IS2

IS3

hCavT1a FERISMLVILLNCVTLGMFRPCEDIACDQRCRILQAFDDFIAFAFVAVEMVVKWALGIFGKKCYLGD TNRLDFFIVIAAGMEYSLDLQNVSFSAVRTV
 rCavT1a FERVSMVLVILLNCVTLGMFRPCEDIACDQRCRILQAFDDFIAFAFVAVEMVVKWALGIFGKKCYLGD TNRLDFFIVIAAGMEYSLDLQNVSFSAVRTV
 hCavT2a FEHVSMVLVIMLNCVTLGMFRPCEDVECGSERCNILEAFDAFIAFAFVAVEMVVKWALGIFGKKCYLGD TNRLDFFIVVAGMEYSLDGHNVSLSAIRTV
 hCavT3 FECVSMVLVILLNCVTLGMYPQCDMDCLSDRCKIMQVDFDFIFIFAMEMVLKMWALGIFGKKCYLGD TNRLDFFIVMAGMEYSLDLQINILSAIRTV
 rCavT3 FECVSMVLVILLNCVTLGMYPQCDMDCLSDRCKILQVDFDFIFIFAMEMVLKMWALGIFGKKCYLGD TNRLDFFIVMAGMEYSLDLQINILSAIRTV

IS4

IS5

hCavT1a RVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LERYYQTENEDESPFICSQPRENGMRS
 rCavT1a RVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LEPYQTENEDESPFICSQPRENGMRS
 hCavT2a RVLRLPLRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLDFAVRNNNTLFLRPYYQTEEGEENPFICSSRRDNGMQK
 hCavT3 RVLRLPLKAINRVPSMRILVNLTLTLLDTPMLGNVLLLCFFVFFIFGIIIGVQLWAGLLRNRCFLEENFTIQGDVA-LPPYYQPEEDDEMPFICSLSGDNGIMG
 rCavT3 RVLRLPLKAINRVPSMRILVNLTLTLLDTPMLGNVLLLCFFVFFIFGIIIGVQLWAGLLRNRCFLEENFTIQGDVA-LPPYYQPEEDDEMPFICSLTGDNGIMG

IP LOOP

hCavT1a CRSVPTLRCGDG-----GGGPPCGLDYEAYNSSNTTCVNNQYYTNC SAGEHNPFKGA INFDNIGYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFYFI
 rCavT1a CRSVPTLRCGE-----GGGPPCSLDYETYNSSNTTCVNNQYYTNC SAGEHNPFKGA INFDNIGYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFYFI
 hCavT2a CSHIPGRDVRMPCTLGWEA-YTQPQAEGVGAARNACINNNQYNNVCRSGDSNPHNGA INFDNTCYAWIAIFQVITLEGWVDIMYVMDAHSFYNFYFI
 hCavT3 CHEIPPLKEQGRECCLSKDDVYDFGAGRODLNASGLCVNNRYNNVCRGTGSANPHKGA INFDNIGYAWIVIFQVITLEGWVEIMYVMDAHSFYNFYFI
 rCavT3 CHEIPPLKEQGRECCLSKDDVYDFGAGRODLNASGLCVNNRYNNVCRGTGTGNANPHKGA INFDNIGYAGIVIFQVITLEGWVEIMYVMDAHSFYNFYFI

IS6

hCavT1a LLIIVGSFFMINCLVVIATQFSETKQRESQILMREQVRFLSNASTLASFSEPGSCYEELLKVLVYILRKAARLAQVSRAAGVRVGLLSSPAPLGQET
 rCavT1a LLIIVGSFFMINCLVVIATQFSETKQRESQILMREQVRFLSNASTLASFSEPGSCYEELLKVLVYILRKAARLAQVSRAIGVRAGLLSSPVARSQEP
 hCavT2a LLIIVGSFFMINCLVVIATQFSETKQRESQILMREQVRFLSNASTLASFSEPGSCYEELLKVLVYILRKAARLAQVSRAIGVRAGLLSSPVARSQEP
 hCavT3 LLIIVGSFFMINCLVVIATQFSETKQREHRLMLEQRQRYLSS-STVASYAEPGDCYEEIFQYVCHILRKAARLAQVSRAIGVRAGLLSSPVARSQEP
 rCavT3 LLIIVGSFFMINCLVVIATQFSETKQREHRLMLEQRQRYLSS-STVASYAEPGDCYEEIFQYVCHILRKAARLAQVSRAIGVRAGLLSSPVARSQEP

Fig. 1A

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hCavT1a QPSSSCSRSHRRLSVHHLVHHHHHHHHHVLGNGTLRAPRASPEIQDRDANGSRRLMLPPPSTPALSAGPPGGA-----ESVHSFYHADCHLEPVRC
rCavT1a QPSGSCTRSHRRLSVHHLVHHHHHHHHHHHVLGNGTLRVPRASPEIQDRDANGSRRLMLPPPSTPSPGPPRGA-----ESVHSFYHADCHLEPVRC
hCavT2a GHRQRACRHTASVHHLVHHHHHHHHHHHVFHSHGSPRRPGPEPGACDTRLVRAGAPSPSPGPGPPDAESVHSIYHADCHIEGPQERARVGTCSRSHCRC
hCavT3 -----
rCavT3 -----

hCavT1a QAPPPRSEASGRTVGSGKVYPTVHTSPPPPETLKEKALVEVAASSGPPPTLTSLN-IPGPGYSSMHKLLLEQTSTGACQSSCKISSPCLKADSGACGPDSC
rCavT1a QAPPPRCPEASGRTVGSGKVYPTVHTSPPPPEILKDKALVEVAPSPGPPPTLTSEN-IPGPGFSSMHKLLLEQTSTGACHSSCKISSPCSKADSGACGPDSC
hCavT2a QPQAGHRAGHHELPHDPALRGGRQQRQHQPRTQCEVGRWTARHRGHGPLSLNSPDPEYKIPHVHAGEHGLQAPGHLGSLSVPCPLSPPPAGTTLTCELKSC
hCavT3 -----
rCavT3 -----

hCavT1a PYCARA-GAGEVELADREMPDSDSEAVYFTQDAQHSDLRDPHS-----RR-QRSLGPDAEPSSVLAFWRLICDTRFKIVDSKYFGRGIM
rCavT1a PYCART-GAGEPEADHVMPDSDSEAVYFTQDAQHSDLRDPHS-----RRQRSLGPDAEPSSVLAFWRLICDTRFKIVDSKYFGRGIM
hCavT2a PYCTRALEDPEGELSGSESGSDGRGVYFTQDVRHGRWDTPRPRAATDPGPGPGSQORRAQORAAPEGPGMGRLLWVTFSGKLRRIVDSKYFSRGIM
hCavT3 PCCQHEGRRPGLGSTDGQEGS-----GSGSSAGGEDEADGDCARSEDGASSELGKEEEEEQADGAVWLCGDVWRETRAKLRGIVDSKYFNRGIM
rCavT3 PHCQHEAGRPPGLGSTDGQEGS-----GSGGSA--EAEANGDGLQSSSEDGVSSDLGKEEQE---DGAARLCGDVWRETRKLRGIVDSKYFNRGIM

IIS1 IIS2 IIS3 IIS4
hCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMILLKLLVYGPFGYIKNPYNIFDGVIVVISVWEIVGQGGGGLSVLRTFRLMRVLKLVRFLLPA
rCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMILLKLLVYGPFGYIKNPYNIFDGVIVVISVWEIVGQGGGGLSVLRTFRLMRVLKLVRFLLPA
hCavT2a MAILVNTLSMGVEXHEQPEELTNALIEISNIVFTSMFALEMILLKLLACGGLGYIRNPYNIFDGIIVISVWEIVGQADGGLSVLRTFRLMRVLKLVRFLLPA
hCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMILLKLLAAGFLDYLRNPYNIFDSIIIVISWEIVGQADGGLSVLRTFRLMRVLKLVRFLLPA
rCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMILLKLLAAGFLDYLRNPYNIFDSIIIVISWEIVGQADGGLSVLRTFRLMRVLKLVRFLLPA

IIS5 IIP LOOP
hCavT1a LQRQLVVLKMTMDNVATFCMLMLFIFIFISILGMHLFGCKEASERD-GDTLPDRKNFDSLMLWAIIVTVFQIILTQEDWNKVLYNGMASTSSWAALYFIALMT
rCavT1a LQRQLVVLKMTMDNVATFCMLMLFIFIFISILGMHLFGCKEASERD-GDTLPDRKNFDSLMLWAIIVTVFQIILTQEDWNKVLYNGMASTSSWAALYFIALMT
hCavT2a LRRQLVVLKMTMDNVATFCMLMLFIFIFISILGMHLFGCKESLRTDGTDPDRKNFDSLMLWAIIVTVFQIILTQEDWNKVLYNGMASTSSWAALYFIALMT
hCavT3 LRRQLVVLKMTMDNVATFCMLMLFIFIFISILGMHIFGCKESLRTDGTDPDRKNFDSLMLWAIIVTVFQIILTQEDWNKVLYNGMASTSSWAALYFIALMT
rCavT3 LRRQLVVLKMTMDNVATFCMLMLFIFIFISILGMHIFGCKESLRTDGTDPDRKNFDSLMLWAIIVTVFQIILTQEDWNKVLYNGMASTTPWASLYFVALMT

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Fig. 1B

IIIS6

hCavT1a FGNVYLFNLLVAILVEGFQAECDANKSESEPDFFSPSLDGDGDRKKCLALVSLGEHPELRKSLPPL-----IIHTAATPMSLPKSTSTGLGEALGPASR
 rCavT1a FGNVYLFNLLVAILVEGFQAECDANKSESEPDFFSPSLDGDGDRKKCLALVSLGEHPELRKSLPPL-----IIHTAATPMSHPKSSSTGVGEALGSGSR
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IIIS5

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Fig. 1C

IIIP LOOP

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IVP LOOP

IVS6

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Fig. 1D

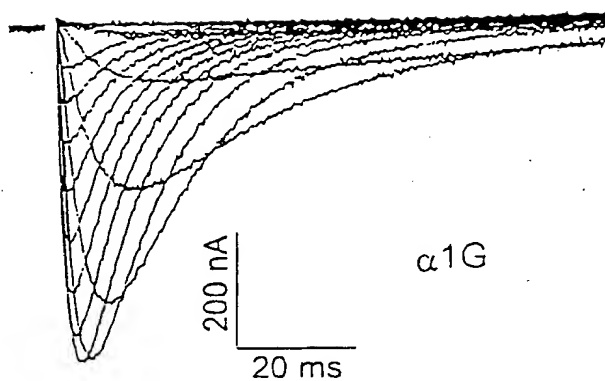
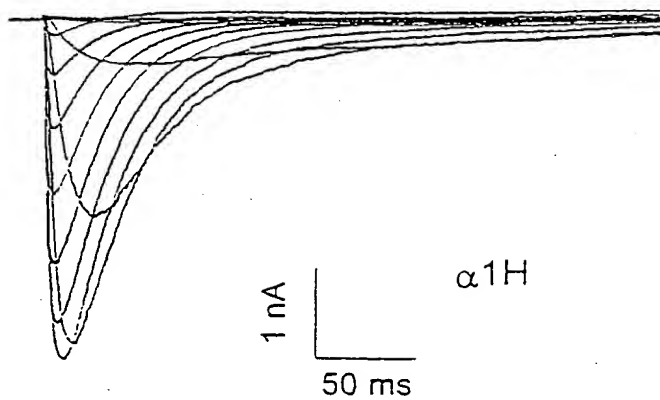
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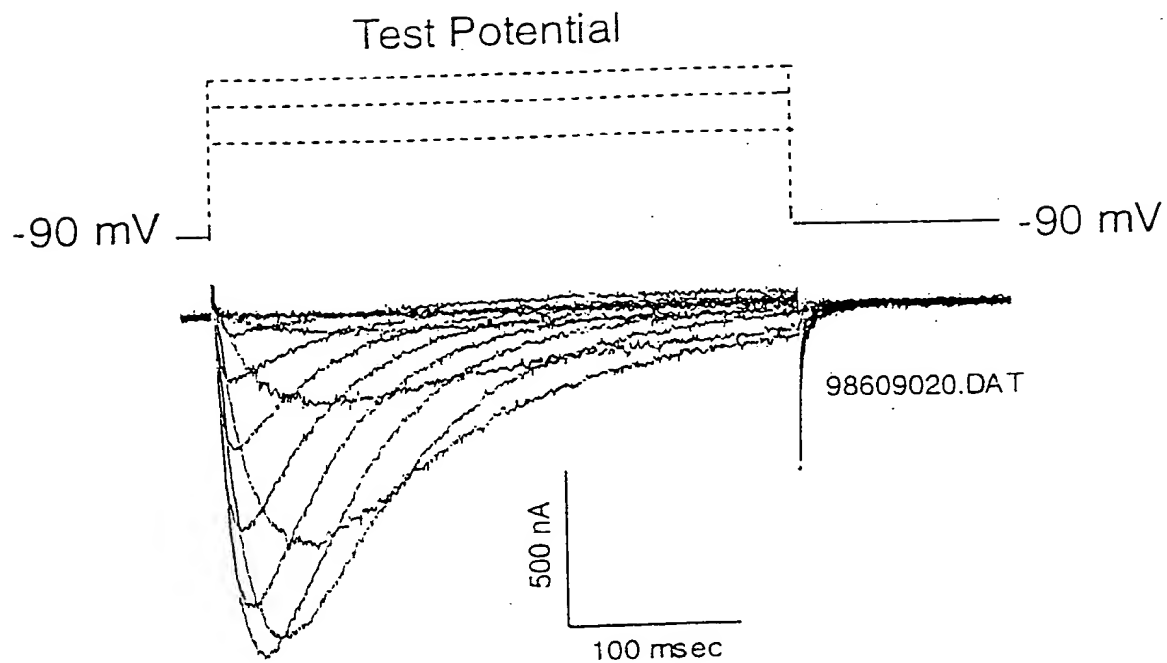
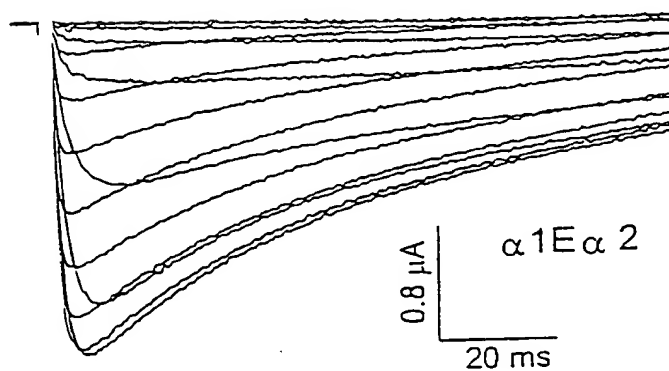
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Fig. 1E

**Figure 2A****Figure 2B**

**Figure 2C****Figure 2D**

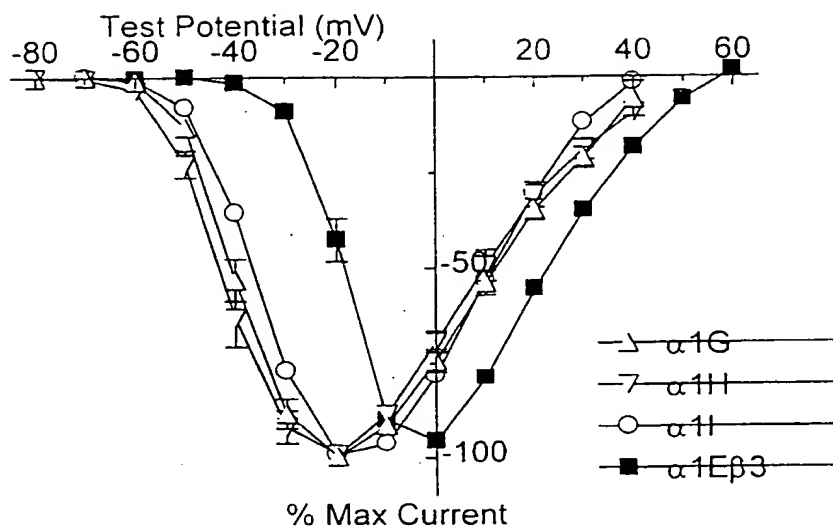


Figure 3A

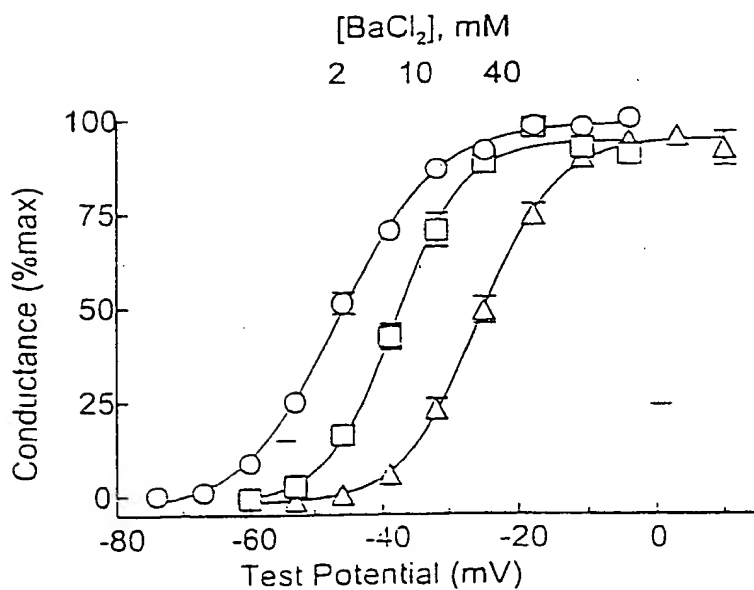
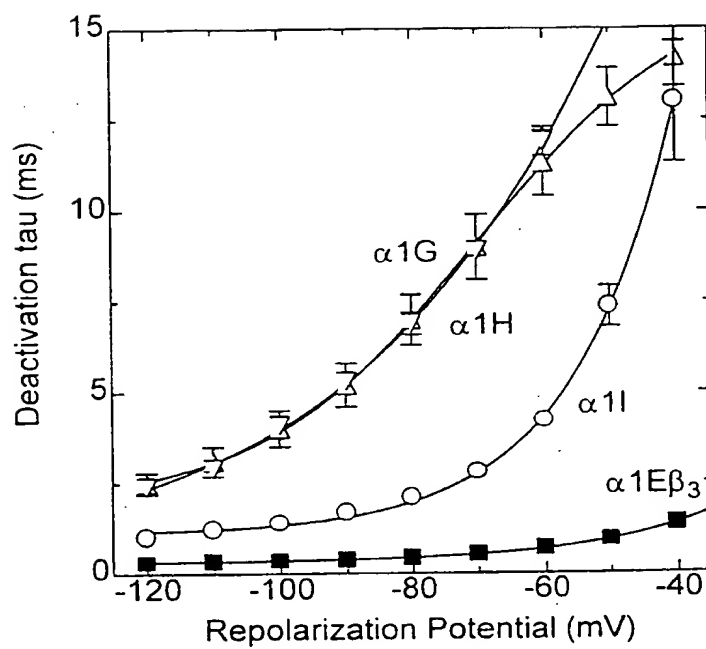
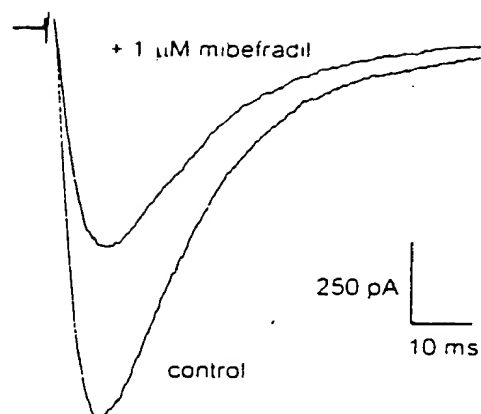
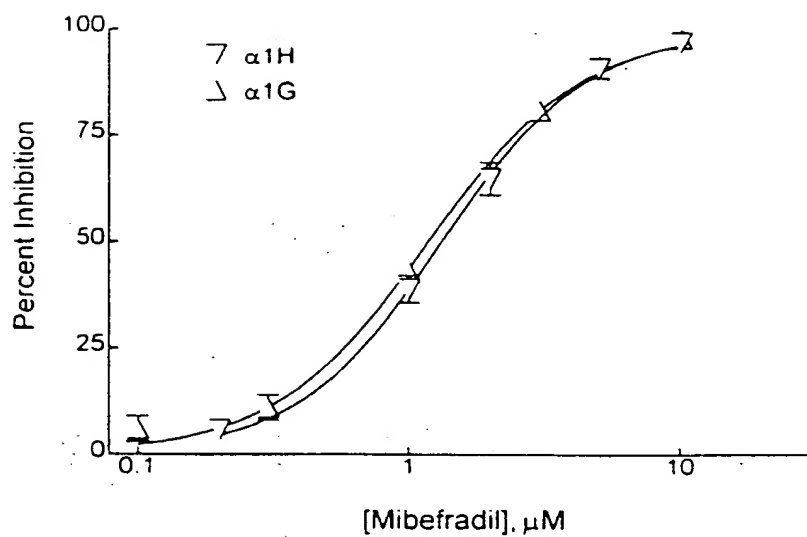


Figure 3B

**Figure 4**

**Figure 5A****Figure 5B**

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5 <110> Perez-Reyes, Edward
 Cribbs, Leanne L.
 Loyola University of Chicago

<120> T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF
 USING SAME

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15 <150> US 08/985,809
 <151> 1997-12-05

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25	agc	tgc	tct	cgc	tcc	cac	cgc	cgc	cta	tcc	gtc	cac	cac	ctg	gtg	cac	1488
	Ser	Cys	Ser	Arg	Ser	His	Arg	Arg	Leu	Ser	Val	His	His	Leu	Val	His	
					485					490					495		
30	cac	cac	cac	cac	cat	cac	cac	cac	tac	cac	ctg	ggc	aat	ggg	acg	ctc	1536
	His	His	His	His	His	His	His	His	Tyr	His	Leu	Gly	Asn	Gly	Thr	Leu	
				500					505					510			
35	agg	gcc	ccc	cgg	gcc	agc	ccg	gag	atc	cag	gac	agg	gat	gcc	aat	ggg	1584
	Arg	Ala	Pro	Arg	Ala	Ser	Pro	Glu	Ile	Gln	Asp	Arg	Asp	Ala	Asn	Gly	
			515					520					525				
	tcc	cgc	cgg	ctc	atg	ctg	cca	cca	ccc	tgc	acg	cct	gcc	ctc	tcc	ggg	1632
	Ser	Arg	Arg	Leu	Met	Leu	Pro	Pro	Pro	Ser	Thr		Ala	Leu	Ser	Gly	
		530					535					540					
40	gcc	ccc	cct	ggc	ggc	gca	gag	tct	gtg	cac	agc	ttc	tac	cat	gcc	gac	1680
	Ala	Pro	Pro	Gly	Gly	Ala	Glu	Ser	Val	His	Ser	Phe	Tyr	His	Ala	Asp	
	545					550					555					560	
45	tgc	cac	tta	gag	cca	gtc	cgc	tgc	cag	gcg	ccc	cct	ccc	agg	tcc	cca	1728
	Cys	His	Leu	Glu	Pro	Val	Arg	Cys	Gln	Ala	Pro	Pro	Pro	Arg	Ser	Pro	
					565					570					575		
50	tct	gag	gca	tcc	ggc	agg	act	gtg	ggc	agc	ggg	aag	gtg	tat	ccc	acc	1776
	Ser	Glu	Ala	Ser	Gly	Arg	Thr	Val	Gly	Ser	Gly	Lys	Val	Tyr	Pro	Thr	
				580					585					590			
55	gtg	cac	acc	agc	cct	cca	ccg	gag	acg	ctg	aag	gag	aag	gca	cta	gta	1824
	Val	His	Thr	Ser	Pro	Pro	Pro	Glu	Thr	Leu	Lys	Glu	Lys	Ala	Leu	Val	
			595					600					605				
	gag	gtg	gct	gcc	agc	tct	ggg	ccc	cca	acc	ctc	acc	agc	ctc	aac	atc	1872
	Glu	Val	Ala	Ala	Ser	Ser	Gly	Pro	Pro	Thr	Leu	Thr	Ser	Leu	Asn	Ile	
		610					615					620					
60	cca	ccc	ggg	ccc	tac	agc	tcc	atg	cac	aag	ctg	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Tyr	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
	625					630					635					640	
	aca	ggc	gcc	tgc	caa	agc	tct	tgc	aag	atc	tcc	agc	cct	tgc	ttg	aaa	1968

	Thr	Gly	Ala	Cys	Gln	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Leu	Lys	
					645					650					655		
5	gca	gac	agt	gga	gcc	tgt	ggc	cca	gac	agc	tgc	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660				665						670			
10	gcc	ggg	gca	ggg	gag	gtg	gag	ctc	gcc	gac	cgt	gaa	atg	cct	gac	tca	2064
	Ala	Gly	Ala	Gly	Glu	Val	Glu	Leu	Ala	Asp	Arg	Glu	Met	Pro	Asp	Ser	
				675				680					685				
15	gac	agc	gag	gca	gtt	tat	gag	ttc	aca	cag	gat	gcc	cag	cac	agc	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
		690					695					700					
20	ctc	cgg	gac	ccc	cac	agc	cgg	cgg	caa	cgg	agc	ctg	ggc	cca	gat	gca	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	Ala	
						710					715					720	
25	gag	ccc	agc	tct	gtg	ctg	gcc	ttc	tgg	agg	cta	atc	tgt	gac	acc	ttc	2208
	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	Phe	
					725				730						735		
30	cga	aag	att	gtg	gac	agc	aag	tac	ttt	ggc	cgg	gga	atc	atg	atc	gcc	2256
	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	Ala	
				740				745						750			
35	atc	ctg	gtc	aac	aca	ctc	agc	atg	ggc	atc	gaa	tac	cac	gag	cag	ccc	2304
	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	Pro	
			755					760					765				
40	gag	gag	ctt	acc	aac	gcc	cta	gaa	atc	agc	aac	atc	gtc	ttc	acc	agc	2352
	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	Ser	
		770					775					780					
45	ctc	ttt	gcc	ctg	gag	atg	ctg	ctg	aag	ctg	ctt	gtg	tat	ggc	ccc	ttt	2400
	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	Phe	
						790				795						800	
50	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggc	gtc	att	gtg	gtc	2448
	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	Val	
					805				810						815		
55	atc	agc	gtg	tgg	gag	atc	gtg	ggc	cag	cag	ggg	ggc	ggc	ctg	tcg	gtg	2496
	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	Val	
				820				825						830			
60	ctg	cgg	acc	ttc	cgc	ctg	atg	cgt	gtg	ctg	aag	ctg	gtg	cgc	ttc	ctg	2544
	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
			835					840					845				
65	cgc	gcg	ctg	cag	cgg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
		850					855					860					
70	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	ttc	agc	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
		865				870				875						880	
75	atc	ctg	ggc	atg	cat	ctc	ttc	ggc	tgc	aag	ttt	gcc	tct	gag	cgg	gat	2688
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	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				900					905					910			
5	atc	gtc	act	gtc	ttt	cag	atc	ctg	acc	cag	gag	gac	tgg	aac	aaa	gtc	2784
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	Val	
				915				920					925				
10	ctc	tac	aat	ggt	atg	gcc	tcc	acg	tcg	tcc	tgg	gcg	gcc	ctt	tat	ttc	2332
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	Phe	
				930			935					940					
15	att	gcc	ctc	atg	acc	ttc	ggc	aac	tac	gtg	ctc	ttc	aat	ttg	ctg	gtc	2880
	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
						950					955					960	
	gcc	att	ctg	gtg	gag	ggc	ttc	cag	gcg	gag	gga	gat	gcc	aac	aag	tcc	2928
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Lys	Ser	
					965					970					975		
20	gaa	tca	gag	ccc	gat	ttc	ttc	tca	ccc	agc	ctg	gat	ggt	gat	ggg	gac	2976
	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp	
				980					985					990			
25	agg	aag	aag	tgc	ttg	gcc	ttg	gtg	tcc	ctg	gga	gag	cac	ccg	gag	ctg	3024
	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu	
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30	cgg	aag	agc	ctg	ctg	ccg	cct	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro	
		1010					1015					1020					
35	atg	tcg	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	gcg	ctg	ggc	3120
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly	
		1025				1030					1035					1040	
	cct	gcg	tcg	cgc	cgc	acc	agc	agc	agc	ggg	tcg	gca	gag	cct	ggg	gcg	3168
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala	
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40	gcc	cac	gag	atg	aag	tca	ccg	ccc	agc	gcc	cgc	agc	tct	ccg	cac	agc	3216
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser	
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45	ccc	tgg	agc	gct	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	cgg	aac	3264
	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	Arg	Asn	
			1075					1080					1085				
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	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu	
		1090				1095					1100						
55	cgg	cgg	tcc	ctg	ttg	tcg	gga	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu	
		1105				1110					1115					1120	
	gag	agc	tca	gaa	gag	gag	cgg	gcc	agc	cct	gcg	ggc	agt	gac	cat	cgc	3408
	Glu	Ser	Ser	Glu	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg	
				1125					1130						1135		
60	cac	agg	ggg	tcc	ctg	gag	cgg	gag	gcc	aag	agt	tcc	ttt	gac	ctg	cca	3456
	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	Leu	Pro	
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	gac	aca	ctg	cag	gtg	cca	ggg	ctg	cat	cgc	act	gcc	agt	ggc	cga	ggg	3504

	Asp	Thr	Leu	Gln	Val	Pro	Gly	Leu	His	Arg	Thr	Ala	Ser	Gly	Arg	Gly	
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	Ser	Ala	Ser	Glu	His	Gln	Asp	Cys	Asn	Gly	Lys	Ser	Ala	Ser	Gly	Arg	
	1170					1175					1180						
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	Leu	Ala	Arg	Ala	Leu	Arg	Pro	Asp	Asp	Pro	Pro	Leu	Asp	Gly	Asp	Asp	
	1185				1190						1195					1200	
15	gcc	gat	gac	gag	ggc	aac	ctg	agc	aaa	ggg	gaa	cgg	gtc	cgc	ggg	tgg	3648
	Ala	Asp	Asp	Glu	Gly	Asn	Leu	Ser	Lys	Gly	Glu	Arg	Val	Arg	Ala	Trp	
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	atc	cga	gcc	cga	ctc	cct	gcc	tgc	tgc	ctc	gag	cga	gac	tcc	tgg	tca	3696
	Ile	Arg	Ala	Arg	Leu	Pro	Ala	Cys	Cys	Leu	Glu	Arg	Asp	Ser	Trp	Ser	
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	Ala	Tyr	Ile	Phe	Pro	Pro	Gln	Ser	Arg	Phe	Arg	Leu	Leu	Cys	His	Arg	
		1235					1240						1245				
25	atc	atc	acc	cac	aag	atg	ttc	gac	cac	gtg	gtc	ctt	gtc	atc	atc	ttc	3792
	Ile	Ile	Thr	His	Lys	Met	Phe	Asp	His	Val	Val	Leu	Val	Ile	Ile	Phe	
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	Leu	Asn	Cys	Ile	Thr	Ile	Ala	Met	Glu	Arg	Pro	Lys	Ile	Asp	Pro	His	
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35	agc	gct	gaa	cgc	atc	ttc	ctg	acc	ctc	tcc	aat	tac	atc	ttc	acc	gca	3888
	Ser	Ala	Glu	Arg	Ile	Phe	Leu	Thr	Leu	Ser	Asn	Tyr	Ile	Phe	Thr	Ala	
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	Val	Phe	Leu	Ala	Glu	Met	Thr	Val	Lys	Val	Val	Ala	Leu	Gly	Trp	Cys	
			1300					1305						1310			
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	Phe	Gly	Glu	Gln	Ala	Tyr	Leu	Arg	Ser	Ser	Trp	Asn	Val	Leu	Asp	Gly	
		1315					1320					1325					
45	ctg	ttg	gtg	ctc	atc	tcc	gtc	atc	gac	att	ctg	gtg	tcc	atg	gtc	tct	4032
	Leu	Leu	Val	Leu	Ile	Ser	Val	Ile	Asp	Ile	Leu	Val	Ser	Met	Val	Ser	
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50	gac	agc	ggc	acc	aag	atc	ctg	ggc	atg	ctg	agg	gtg	ctg	cgg	ctg	ctg	4080
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55	cgg	acc	ctg	cgc	ccg	ctc	agg	gtg	atc	agc	cgg	gcg	cag	ggg	ctg	aag	4128
	Arg	Thr	Leu	Arg	Pro	Leu	Arg	Val	Ile	Ser	Arg	Ala	Gln	Gly	Leu	Lys	
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	Leu	Val	Val	Glu	Thr	Leu	Met	Ser	Ser	Leu	Lys	Pro	Ile	Gly	Asn	Ile	
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	Val	Val	Ile	Cys	Cys	Ala	Phe	Phe	Ile	Ile	Phe	Gly	Ile	Leu	Gly	Val	
		1395					1400					1405					
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	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Phe	Val	Cys	Gln	Gly	Glu	Asp	Thr	Arg	
	1410						1415					1420					
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	Arg	His	Lys	Tyr	Asn	Phe	Asp	Asn	Leu	Gly	Gln	Ala	Leu	Met	Ser	Leu	
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15	ttc	gtt	ttg	gcc	tcc	aag	gat	ggt	tgg	gtg	gac	atc	atg	tac	gat	ggg	4416
	Phe	Val	Leu	Ala	Ser	Lys	Asp	Gly	Trp	Val	Asp	Ile	Met	Tyr	Asp	Gly	
			1460						1465					1470			
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	Leu	Asp	Ala	Val	Gly	Val	Asp	Gln	Gln	Pro	Ile	Met	Asn	His	Asn	Pro	
			1475					1480					1485				
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	Trp	Met	Leu	Leu	Tyr	Phe	Ile	Ser	Phe	Leu	Leu	Ile	Val	Ala	Phe	Phe	
	1490						1495					1500					
25	gtc	ctg	aac	atg	ttt	gtg	ggt	gtg	gtg	gtg	gag	aac	ttc	cac	aag	tgt	4560
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	Arg	Gln	His	Gln	Glu	Glu	Glu	Glu	Ala	Arg	Arg	Arg	Glu	Glu	Lys	Arg	
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35	cta	cga	aga	ctg	gag	aaa	aag	aga	agg	agt	aag	gag	aag	cag	atg	gct	4656
	Leu	Arg	Arg	Leu	Glu	Lys	Lys	Arg	Arg	Ser	Lys	Glu	Lys	Gln	Met	Ala	
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	Glu	Ala	Gln	Cys	Lys	Pro	Tyr	Tyr	Ser	Asp	Tyr	Ser	Arg	Phe	Arg	Leu	
		1555						1560					1565				
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45	ggt	gtc	atc	ggg	ctg	aac	gtg	gtc	acc	atg	gcc	atg	gag	cac	tac	cag	4800
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	Gln	Pro	Gln	Ile	Leu	Asp	Glu	Ala	Leu	Lys	Ile	Cys	Asn	Tyr	Ile	Phe	
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55	act	gtc	atc	ttt	gtc	ttg	gag	tca	gtt	ttc	aaa	ctt	gtg	gcc	ttt	ggt	4896
	Thr	Val	Ile	Phe	Val	Leu	Glu	Ser	Val	Phe	Lys	Leu	Val	Ala	Phe	Gly	
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	Phe	Arg	Arg	Phe	Phe	Gln	Asp	Arg	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Ile	
		1635						1640					1645				
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	Ala	Ser	Leu	Pro	Ile	Asn	Pro	Thr	Ile	Ile	Arg	Ile	Met	Arg	Val	Leu	
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	Pro	Trp	Phe	Glu	Arg	Ile	Ser	Met	Leu	Val	Ile	Leu	Leu	Asn	Cys	Val	
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	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp			
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	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu			
			995				1000						1005						
30	cgg	aag	agc	ctg	ctg	ccg	cct	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072		
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro			
	1010					1015						1020							
35	atg	tcg	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	gcg	ctg	ggc	3120		
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly			
	1025				1030					1035					1040				
40	cct	gcg	tcg	cgc	cgc	acc	agc	agc	agc	ggg	tcg	gca	gag	cct	ggg	gcg	3168		
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala			
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45	gcc	cac	gag	atg	aag	tca	ccg	ccc	agc	gcc	cgc	agc	tct	ccg	cac	agc	3216		
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser			
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	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	Arg	Asn			
		1075					1080					1085							
55	agc	ctc	ggc	cgt	gca	ccc	agc	ctg	aag	cgg	aga	agc	cca	agt	gga	gag	3312		
	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu			
	1090					1095					1100								
60	cgg	cgg	tcc	ctg	ttg	tcg	gga	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360		
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu			
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	Glu	Ser	Ser	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg				
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70	cac	agg	ggg	tcc	ctg	gag	cgg	gag	gcc	aag	agt	tcc	ttt	gac	ctg	cca	3456		
	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	Leu	Pro			
			1140					1145					1150						
75	gac	aca	ctg	cag	gtg	cca	ggg	ctg	cat	cgc	act	gcc	agt	ggc	cga	ggg	3504		
	Asp	Thr	Leu	Gln	Val	Pro	Gly	Leu	His	Arg	Thr	Ala	Ser	Gly	Arg	Gly			

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10	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp 1185 1190 1195 1200			3600
15	gcc gat gac gag ggc aac ctg agc aaa ggg gaa cgg gtc cgc gcg tgg Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp 1205 1210 1215			3648
20	atc cga gcc cga ctc cct gcc tgc tgc ctc gag cga gac tcc tgg tca Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser 1220 1225 1230			3696
25	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctc ctg tgt cac cgg Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg 1235 1240 1245			3744
30	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe 1250 1255 1260			3792
35	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His 1265 1270 1275 1280			3840
40	agc gct gaa cgc atc ttc ctg acc ctc tcc aat tac atc ttc acc gca Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala 1285 1290 1295			3888
45	gtc ttt ctg gct gaa atg aca gtg aag gtg gtg gca ctg ggc tgg tgc Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly Trp Cys 1300 1305 1310			3936
50	ttc ggg gag cag gcg tac ctg cgg agc agt tgg aac gtg ctg gac ggg Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu Asp Gly 1315 1320 1325			3984
55	ctg ttg gtg ctc atc tcc gtc atc gac att ctg gtg tcc atg gtc tct Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser 1330 1335 1340			4032
60	gac agc ggc acc aag atc ctg ggc atg ctg agg gtg ctg cgg ctg ctg Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu 1345 1350 1355 1360			4080
65	cgg acc ctg cgc ccg ctc agg gtg atc agc cgg gcg cag ggg ctg aag Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly Leu Lys 1365 1370 1375			4128
70	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa ccc atc ggc aac att Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile 1380 1385 1390			4176
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	ttc gtt ttg gcc tcc aag gat ggt tgg gtg gac atc atg tac gat ggg Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr Asp Gly 1460 1465 1470	4416		
15	ctg gat gct gtg ggc gtg gac cag cag ccc atc atg aac cac aac ccc Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His Asn Pro 1475 1480 1485	4464		
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5	aac ccc acc atc atc cgc atc atg agg gtg ctg cgc att gcc cga gtg Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg Val	1685	1690	1695	5088
10	ctg aag ctg ctg aag atg gct gtg ggc atg cgg gcg ctg ctg gac acg Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg Ala Leu Leu Asp Thr	1700	1705	1710	5136
15	gtg atg cag gcc ctg ccc cag gtg ggg aac ctg gga ctt ctc ttc atg Val Met Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe Met	1715	1720	1725	5184
20	ttg ttg ttt ttc atc ttt gca gct ctg ggc gtg gag ctc ttt gga gac Leu Leu Phe Phe Ile Phe Ala Ala Leu Gly Val Glu Leu Phe Gly Asp	1730	1735	1740	5232
25	ctg gag tgt gac gag aca cac ccc tgt gag ggc ctg ggc cgt cat gcc Leu Glu Cys Asp Glu Thr His Pro Cys Glu Gly Leu Gly Arg His Ala	1745	1750	1755	5280
30	acc ttt cgg aac ttt ggc atg gcc ttc cta acc ctc ttc cga gtc tcc Thr Phe Arg Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val Ser	1765	1770	1775	5328
35	aca ggt gac aat tgg aat ggc att atg aag gac acc ctc cgg gac tgt Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Asp Cys	1780	1785	1790	5376
40	gac cag gag tcc acc tgc tac aac acg gtc atc tcg cct atc tac ttt Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val Ile Ser Pro Ile Tyr Phe	1795	1800	1805	5424
45	gtg tcc ttc gtg ctg acg gcc cag ttc gtg cta gtc aac gtg gtg atc Val Ser Phe Val Leu Thr Ala Gln Phe Val Leu Val Asn Val Val Ile	1810	1815	1820	5472
50	gcc gtg ctg atg aag cac ctg gag gag agc aac aag gag gcc aag gag Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys Glu Ala Lys Glu	1825	1830	1835	5520
55	gag gcc gag cta gag gct gag ctg gag ctg gag atg aag acc ctc agc Glu Ala Glu Leu Glu Ala Glu Leu Glu Leu Glu Met Lys Thr Leu Ser	1845	1850	1855	5568
60	ccc cag ccc cac tcg cca ctg ggc agc ccc ttc ctc tgg cct ggg gtc Pro Gln Pro His Ser Pro Leu Gly Ser Pro Phe Leu Trp Pro Gly Val	1860	1865	1870	5616
65	gag ggc ccc gac agc ccc gac agc ccc aag cct ggg gct ctg cac cca Glu Gly Pro Asp Ser Pro Asp Ser Pro Lys Pro Gly Ala Leu His Pro	1875	1880	1885	5664
70	gcg gcc cac gcg aga tca gcc tcc cac ttt tcc ctg gag cac ccc acg Ala Ala His Ala Arg Ser Ala Ser His Phe Ser Leu Glu His Pro Thr	1890	1895	1900	5712
75	atg cag ccc cac ccc acg gag ctg cca gga cca gac tta ctg act gtg Met Gln Pro His Pro Thr Glu Leu Pro Gly Pro Asp Leu Leu Thr Val	1905	1910	1915	5760
80	cgg aag tct ggg gtc agc cga acg cac tct ctg ccc aat gac agc tac Arg Lys Ser Gly Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr				5808

	1925	1930	1935	
5	atg tgt cgg cat ggg agc act gcc gag ggg ccc ctg gga cac agg ggc Met Cys Arg His Gly Ser Thr Ala Glu Gly Pro Leu Gly His Arg Gly 1940 1945 1950	5856		
10	tgg ggg ctc ccc aaa gct cag tca ggc tcc gtc ttg tcc gtt cac tcc Trp Gly Leu Pro Lys Ala Gln Ser Gly Ser Val Leu Ser Val His Ser 1955 1960 1965	5904		
15	cag cca gca gat acc agc tac atc ctg cag ctt ccc aaa gat gca cct Gln Pro Ala Asp Thr Ser Tyr Ile Leu Gln Leu Pro Lys Asp Ala Pro 1970 1975 1980	5952		
20	cat ctg ctc cag ccc cac agc gcc cca acc tgg ggc acc atc ccc aaa His Leu Leu Gln Pro His Ser Ala Pro Thr Trp Gly Thr Ile Pro Lys 1985 1990 1995 2000	6000		
25	ctg ccc cca cca gga cgc tcc cct ttg gct cag agg cca ctc agg cgc Leu Pro Pro Pro Gly Arg Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg 2005 2010 2015	6048		
30	cag gca gca ata agg act gac tcc ttg gac gtt cag ggt ctg ggc agc Gln Ala Ala Ile Arg Thr Asp Ser Leu Asp Val Gln Gly Leu Gly Ser 2020 2025 2030	6096		
35	cgg gaa gac ctg ctg gca gag gtg agt ggg ccc tcc ccg ccc ctg gcc Arg Glu Asp Leu Leu Ala Glu Val Ser Gly Pro Ser Pro Pro Leu Ala 2035 2040 2045	6144		
40	cgg gcc tac tct ttc tgg ggc cag tca agt acc cag gca cag cag cac Arg Ala Tyr Ser Phe Trp Gly Gln Ser Ser Thr Gln Ala Gln Gln His 2050 2055 2060	6192		
45	tcc cgc agc cac agc aag atc tcc aag cac atg acc ccg cca gcc cct Ser Arg Ser His Ser Lys Ile Ser Lys His Met Thr Pro Pro Ala Pro 2065 2070 2075 2080	6240		
50	tgc cca ggc cca gaa ccc aac tgg ggc aag ggc cct cca gag acc aga Cys Pro Gly Pro Glu Pro Asn Trp Gly Lys Gly Pro Pro Glu Thr Arg 2085 2090 2095	6288		
55	agc agc tta gag ttg gac acg gag ctg agc tgg att tca gga gac ctc Ser Ser Leu Glu Leu Asp Thr Glu Leu Ser Trp Ile Ser Gly Asp Leu 2100 2105 2110	6336		
60	ctg ccc cct ggc ggc cag gag gag ccc cca tcc cca cgg gac ctg aag Leu Pro Pro Gly Gly Gln Glu Glu Pro Pro Ser Pro Arg Asp Leu Lys 2115 2120 2125	6384		
65	aag tgc tac agc gtg gag gcc cag agc tgc cag cgc cgg cct acg tcc Lys Cys Tyr Ser Val Glu Ala Gln Ser Cys Gln Arg Arg Pro Thr Ser 2130 2135 2140	6432		
70	tgg ctg gat gag cag agg aga cac tct atc gcc gtc agc tgc ctg gac Trp Leu Asp Glu Gln Arg Arg His Ser Ile Ala Val Ser Cys Leu Asp 2145 2150 2155 2160	6480		
75	agc ggc tcc caa ccc cac ctg ggc aca gac ccc tct aac ctt ggg ggc Ser Gly Ser Gln Pro His Leu Gly Thr Asp Pro Ser Asn Leu Gly Gly 2165 2170 2175	6528		
80	cag cct ctt ggg ggg cct ggg agc cgg ccc aag aaa aaa ctc agc ccg Gln Pro Leu Gly Gly Pro Gly Ser Arg Pro Lys Lys Lys Leu Ser Pro 2180 2185 2190	6576		

	2180	2185	2190	
5	cct agt atc acc ata gac ccc ccc gag agc caa ggt cct cgg acc cgg Pro Ser Ile Thr Ile Asp Pro Pro Glu Ser Gln Gly Pro Arg Thr Pro	2195	2200	2205 6624
10	ccc agc cct ggt atc tgc ctc cgg agg agg gct cgg tcc agc gac tcc Pro Ser Pro Gly Ile Cys Leu Arg Arg Arg Ala Pro Ser Ser Asp Ser	2210	2215	2220 6672
15	aag gat ccc ttg gcc tct ggc ccc cct gac agc atg gct gcc tcg ccc Lys Asp Pro Leu Ala Ser Gly Pro Pro Asp Ser Met Ala Ala Ser Pro	2225	2230	2235 2240 6720
20	tcc cca aag aaa gat gtg ctg agt ctc tcc ggt tta tcc tct gac cca Ser Pro Lys Lys Asp Val Leu Ser Leu Ser Gly Leu Ser Ser Asp Pro	2245	2250	2255 6768
25	gca gac ctg gac ccc Ala Asp Leu Asp Pro	2260		6783
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45	cgg agc ttc atg cgg ctc aac gac ctg tcg ggg gcc ggg ggg cgg ccg Arg Ser Phe Met Arg Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Pro	20	25	30 96
50	ggg ccg ggg tca gca gaa aag gac ccg ggc agc gcg gac tcc gag gcg Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	35	40	45 144
55	gag ggg ctg ccg tac ccg gcg ctg gcc ccg gtg gtt ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	50	55	60 192
60	agc cag gac agc cgc ccg cgg agc tgg tgt ctc cgc acg gtc tgt aac Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn	65	70	75 80 240
65	ccc tgg ttt gag cgc atc agc atg ttg gtc atc ctt ctc aac tgc gtg Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val	85	90	95 288
70	acc ctg ggc atg ttc cgg oca tgc gag gac atc gcc tgt gac tcc cag Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	100	105	110 336
75	cgc tgc cgg atc ctg cag gcc ttt gat gac ttc atc ttt gcc ttc ttt Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe	115	120	125 384

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	Ala	Val	Glu	Met	Val	Val	Lys	Met	Val	Ala	Leu	Gly	Ile	Phe	Gly	Lys	
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10	aag	tgt	tac	ctg	gga	gac	act	tgg	aac	cgg	ctt	gac	att	ttc	atc	gtc	480
	Lys	Cys	Tyr	Leu	Gly	Asp	Thr	Trp	Asn	Arg	Leu	Asp	Phe	Phe	Ile	Val	
	145					150					155					160	
15	atc	gca	ggg	atg	ctg	gag	tac	tgg	ctg	gac	ctg	cag	aac	gtc	agc	ttc	528
	Ile	Ala	Gly	Met	Leu	Glu	Tyr	Ser	Leu	Asp	Leu	Gln	Asn	Val	Ser	Phe	
					165					170					175		
20	tca	gct	gtc	agg	aca	gtc	cgt	gtg	ctg	cga	cgg	ctc	agg	gcc	att	aac	576
	Ser	Ala	Val	Arg	Thr	Val	Arg	Val	Leu	Arg	Pro	Leu	Arg	Ala	Ile	Asn	
				180					185					190			
25	cgg	gtg	ccc	agc	atg	cgc	atc	ctt	gtc	acg	tgg	ctg	ctg	gat	acg	ctg	624
	Arg	Val	Pro	Ser	Met	Arg	Ile	Leu	Val	Thr	Leu	Leu	Leu	Asp	Thr	Leu	
			195					200					205				
30	ccc	atg	ctg	ggc	aac	gtc	ctg	ctg	ctc	tgc	ttc	ttc	gtc	ttc	ttc	atc	672
	Pro	Met	Leu	Gly	Asn	Val	Leu	Leu	Leu	Cys	Phe	Phe	Val	Phe	Phe	Ile	
		210					215					220					
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	Phe	Gly	Ile	Val	Gly	Val	Gln	Leu	Trp	Ala	Gly	Leu	Leu	Arg	Asn	Arg	
	225				230					235					240		
40	tgc	ttc	cta	cct	gag	aat	ttc	agc	ctc	ccc	ctg	agc	gtg	gac	ctg	gag	768
	Cys	Phe	Leu	Pro	Glu	Asn	Phe	Ser	Leu	Pro	Leu	Ser	Val	Asp	Leu	Glu	
					245					250					255		
45	cgc	tat	tac	cag	aca	gag	aac	gag	gat	gag	agc	ccc	ttc	atc	tgc	tcc	816
	Arg	Tyr	Tyr	Gln	Thr	Glu	Asn	Glu	Asp	Glu	Ser	Pro	Phe	Ile	Cys	Ser	
				260					265					270			
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	Gln	Pro	Arg	Glu	Asn	Gly	Met	Arg	Ser	Cys	Arg	Ser	Val	Pro	Thr	Leu	
			275					280					285				
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	Arg	Gly	Asp	Gly	Gly	Gly	Gly	Pro	Pro	Cys	Gly	Leu	Asp	Tyr	Glu	Ala	
		290				295						300					
60	tac	aac	agc	tcc	agc	aac	acc	acc	tgt	gtc	aac	tgg	aac	cag	tac	tac	960
	Tyr	Asn	Ser	Ser	Ser	Asn	Thr	Thr	Cys	Val	Asn	Trp	Asn	Gln	Tyr	Tyr	
	305					310					315					320	
65	acc	aac	tgc	tca	gcg	ggg	gag	cac	aac	ccc	ttc	aag	ggc	gcc	atc	aac	1008
	Thr	Asn	Cys	Ser	Ala	Gly	Glu	His	Asn	Pro	Phe	Lys	Gly	Ala	Ile	Asn	
					325					330					335		
70	ttt	gac	aac	att	ggc	tat	gcc	tgg	atc	gcc	atc	ttc	cag	gtc	atc	acg	1056
	Phe	Asp	Asn	Ile	Gly	Tyr	Ala	Trp	Ile	Ala	Ile	Phe	Gln	Val	Ile	Thr	
				340				345						350			
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	Leu	Glu	Gly	Trp	Val	Asp	Ile	Met	Tyr	Phe	Val	Met	Asp	Ala	His	Ser	
			355					360					365				
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	Phe	Tyr	Asn	Phe	Ile	Tyr	Phe	Ile	Leu	Leu	Ile	Ile	Val	Gly	Ser	Phe	
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 Arg Ser Phe Met Arg Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Pro
 20 25 30

55 ggg ccg ggg tca gca gaa aag gac ccg ggc agc gcg gac tcc gag gcg 144
 Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
 35 40 45

60 gag ggg ctg ccg tac ccg gcg ctg gcc ccg gtg gtt ttc ttc tac ttg 192
 Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
 50 55 60

65 agc cag gac agc cgc ccg cgg agc tgg tgt ctc cgc acg gtc tgt aac 240
 Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
 65 70 75 80

70 ccc tgg ttt gag cgc atc agc atg ttg gtc atc ctt ctc aac tgc gtg 288
 Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val
 85 90 95

75 acc ctg ggc atg ttc cgg cca tgc gag gac atc gcc tgt gac tcc cag 336
 Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
 100 105 110

	cgc tgc cgg att ctg cag gcc ttt gat gac ttc atc ttt gcc ttc ttt	384
	Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe	
	115 120 125	
5	gcc gtg gag atg gtg gtg aag atg gtg gcc ttg gcc atc ttt ggg aaa	432
	Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys	
	130 135 140	
10	aag tgt tac ctg gga gac act tgg aac cgg ctt gac ttt ttc atc gtc	480
	Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val	
	145 150 155 160	
15	atc gca ggg atg ctg gag tac tgg ctg gac ctg cag aac gtc agc ttc	528
	Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe	
	165 170 175	
20	tca gct gtc agg aca gtc cgt gtg ctg cga ccg ctc agg gcc att aac	576
	Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn	
	180 185 190	
25	cgg gtg ccc agc atg cgc atc ctt gtc acg ttg ctg ctg gat acg ctg	624
	Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu	
	195 200 205	
30	ccc atg ctg ggc aac gtc ctg ctg ctc tgc ttc ttc gtc ttc ttc atc	672
	Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile	
	210 215 220	
35	ttc ggc atc gtc ggc gtc cag ctg tgg gca ggg ctg ctt cgg aac cga	720
	Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg	
	225 230 235 240	
40	tgc ttc cta cct gag aat ttc agc ctc ccc ctg agc gtg gac ctg gag	768
	Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu	
	245 250 255	
45	cgc tat tac cag aca gag aac gag gat gag agc ccc ttc atc tgc tcc	816
	Arg Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser	
	260 265 270	
50	cag cca cgc gag aac ggc atg cgg tcc tgc aga agc gtg ccc acg ctg	864
	Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu	
	275 280 285	
55	cgc ggg gac ggg ggc ggt ggc cca cct tgc ggt ctg gac tat gag gcc	912
	Arg Gly Asp Gly Gly Gly Gly Pro Pro Cys Gly Leu Asp Tyr Glu Ala	
	290 295 300	
60	tac aac agc tcc agc aac acc acc tgt gtc aac tgg aac cag tac tac	960
	Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr	
	305 310 315 320	
65	acc aac tgc tca gcg ggg gag cac aac ccc ttc aag ggc gcc atc aac	1008
	Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn	
	325 330 335	
70	ttt gac aac att ggc tat gcc tgg atc gcc atc ttc cag gtc atc acg	1056
	Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr	
	340 345 350	
75	ctg gag ggc tgg gtc gac atc atg tac ttt gtg atg gat gct cat tcc	1104
	Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser	
	355 360 365	

	ttc	tac	aat	ttc	atc	tac	ttc	atc	ctc	ctc	atc	atc	gtg	ggc	tcc	ttc	1152
	Phe	Tyr	Asn	Phe	Ile	Tyr	Phe	Ile	Leu	Leu	Ile	Ile	Val	Gly	Ser	Phe	
	370						375					380					
5	ttc	atg	atc	aac	ctg	tgc	ctg	gtg	gtg	att	gcc	acg	cag	ttc	tca	gag	1200
	Phe	Met	Ile	Asn	Leu	Cys	Leu	Val	Val	Ile	Ala	Thr	Gln	Phe	Ser	Glu	
	385					390					395					400	
10	acc	aag	cag	ggg	gaa	agc	cag	ctg	atg	cgg	gag	cag	cgt	gtg	ggg	ttc	1248
	Thr	Lys	Gln	Arg	Glu	Ser	Gln	Leu	Met	Arg	Glu	Gln	Arg	Val	Arg	Phe	
					405					410					415		
15	ctg	tcc	aac	gcc	agc	acc	ctg	gct	agc	ttc	tct	gag	ccc	ggc	agg	tgc	1296
	Leu	Ser	Asn	Ala	Ser	Thr	Leu	Ala	Ser	Phe	Ser	Glu	Pro	Gly	Ser	Cys	
				420					425					430			
20	tat	gag	gag	ctg	ctc	aag	tac	ctg	gtg	tac	atc	ctt	cgt	aag	gca	gcc	1344
	Tyr	Glu	Glu	Leu	Leu	Lys	Tyr	Leu	Val	Tyr	Ile	Leu	Arg	Lys	Ala	Ala	
				435				440					445				
25	cgc	agg	ctg	gct	cag	gtc	tct	cgg	gca	gca	ggg	gtg	cgg	gtt	ggg	ctg	1392
	Arg	Arg	Leu	Ala	Gln	Val	Ser	Arg	Ala	Ala	Gly	Val	Arg	Val	Gly	Leu	
	450						455					460					
30	ctc	agc	agc	cca	gca	ccc	ctc	ggg	ggc	cag	gag	acc	cag	ccc	agg	agc	1440
	Leu	Ser	Ser	Pro	Ala	Pro	Leu	Gly	Gly	Gln	Glu	Thr	Gln	Pro	Ser	Ser	
	465					470					475					480	
35	agc	tgc	tct	cgc	tcc	cac	cgc	cgc	cta	tcc	gtc	cac	cac	ctg	gtg	cac	1488
	Ser	Cys	Ser	Arg	Ser	His	Arg	Arg	Leu	Ser	Val	His	His	Leu	Val	His	
					485					490					495		
40	cac	cac	cac	cac	cat	cac	cac	cac	tac	cac	ctg	ggc	aat	ggg	acg	ctc	1536
	His	His	His	His	His	His	His	His	Tyr	His	Leu	Gly	Asn	Gly	Thr	Leu	
				500					505					510			
45	agg	gcc	ccc	cgg	gcc	agc	ccg	gag	atc	cag	gac	agg	gat	gcc	aac	ggg	1584
	Arg	Ala	Pro	Arg	Ala	Ser	Pro	Glu	Ile	Gln	Asp	Arg	Asp	Ala	Asn	Gly	
			515					520					525				
50	tcc	cgc	cgg	ctc	atg	ctg	cca	cca	ccc	tgc	acg	cct	gcc	ctc	tcc	ggg	1632
	Ser	Arg	Arg	Leu	Met	Leu	Pro	Pro	Pro	Ser	Thr	Pro	Ala	Leu	Ser	Gly	
	530						535					540					
55	gcc	ccc	cct	ggg	ggc	gca	gag	tct	gtg	cac	agc	ttc	tac	cat	gcc	gac	1680
	Ala	Pro	Pro	Gly	Gly	Ala	Glu	Ser	Val	His	Ser	Phe	Tyr	His	Ala	Asp	
	545					550					555					560	
60	tgc	cac	tta	gag	cca	gtc	cgc	tgc	cag	gcg	ccc	cct	ccc	agg	tcc	cca	1728
	Cys	His	Leu	Glu	Pro	Val	Arg	Cys	Gln	Ala	Pro	Pro	Pro	Arg	Ser	Pro	
					565					570					575		
65	tct	gag	gca	tcc	ggc	agg	act	gtg	ggc	agc	ggg	aag	gtg	tat	ccc	acc	1776
	Ser	Glu	Ala	Ser	Gly	Arg	Thr	Val	Gly	Ser	Gly	Lys	Val	Tyr	Pro	Thr	
				580					585					590			
70	gtg	cac	acc	agc	cct	cca	ccg	gag	acg	ctg	aag	gag	aag	gca	cta	gta	1824
	Val	His	Thr	Ser	Pro	Pro	Pro	Glu	Thr	Leu	Lys	Glu	Lys	Ala	Leu	Val	
			595					600					605				
75	gag	gtg	gct	gcc	agc	tct	ggg	ccc	cca	acc	ctc	acc	agc	ctc	aac	atc	1872
	Glu	Val	Ala	Ala	Ser	Ser	Gly	Pro	Pro	Thr	Leu	Thr	Ser	Leu	Asn	Ile	
	610						615					620					

	cca	ccc	ggg	ccc	tac	agc	tcc	atg	cac	aag	ctg	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Tyr	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
	625					630					635					640	
5	aca	ggt	gcc	tgc	caa	agc	tct	tgc	aag	atc	tcc	agc	cct	tgc	ttg	aaa	1968
	Thr	Gly	Ala	Cys	Gln	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Leu	Lys	
					645					650					655		
10	gca	gac	agt	gga	gcc	tgt	ggt	cca	gac	agc	tgc	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660					665					670			
15	gcc	ggg	gca	ggg	gag	gtg	gag	ctc	gcc	gac	cgt	gaa	atg	cct	gac	tca	2064
	Ala	Gly	Ala	Gly	Glu	Val	Glu	Leu	Ala	Asp	Arg	Glu	Met	Pro	Asp	Ser	
			675					680					685				
20	gac	agc	gag	gca	gtt	tat	gag	ttc	aca	cag	gat	gcc	cag	cac	agc	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
	690						695					700					
25	ctc	cgg	gac	ccc	cac	agc	cgg	cgg	caa	cgg	agc	ctg	ggc	cca	gat	gca	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	Ala	
	705					710					715					720	
30	gag	ccc	agc	tct	gtg	ctg	gcc	ttc	tgg	agg	cta	atc	tgt	gac	acc	ttc	2208
	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	Phe	
					725				730						735		
35	cga	aag	att	gtg	gac	agc	aag	tac	ttt	ggc	cgg	gga	atc	atg	atc	gcc	2256
	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	Ala	
				740					745					750			
40	atc	ctg	gtc	aac	aca	ctc	agc	atg	ggc	atc	gaa	tac	cac	gag	cag	ccc	2304
	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	Pro	
			755					760					765				
45	gag	gag	ctt	acc	aac	gcc	cta	gaa	atc	agc	aac	atc	gtc	ttc	acc	agc	2352
	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	Ser	
		770					775					780					
50	ctc	ttt	gcc	ctg	gag	atg	ctg	ctg	aag	ctg	ctt	gtg	tat	ggt	ccc	ttt	2400
	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	Phe	
	785					790					795					800	
55	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggt	gtc	att	gtg	gtc	2448
	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	Val	
					805					810					815		
60	atc	agc	gtg	tgg	gag	atc	gtg	ggc	cag	cag	ggg	ggc	ggc	ctg	tgg	gtg	2496
	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	Val	
				820					825					830			
65	ctg	cgg	acc	ttc	cgc	ctg	atg	cgt	gtg	ctg	aag	ctg	gtg	cgc	ttc	ctg	2544
	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
			835					840					845				
70	ccg	gcg	ctg	cag	cgg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
		850					855					860					
75	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	ttc	agc	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
	865					870					875					880	

	atc	ctg	ggc	atg	cat	ctc	ttc	ggc	tgc	aag	ttt	gcc	tct	gag	cgg	gat	2683
	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Glu	Arg	Asp	
				285						390					895		
5	ggg	gac	acc	ctg	cca	gac	cgg	aag	aat	ttt	gac	tcc	ttg	ctc	tgg	gcc	2736
	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				900					905					910			
10	atc	gtc	act	gtc	ttc	cag	atc	ctg	acc	cag	gag	gac	tgg	aac	aaa	gtc	2784
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	Val	
				915				920					925				
15	ctc	tac	aat	ggt	atg	gcc	tcc	acg	tgc	tcc	tgg	gcg	gcc	cct	tat	ttc	2832
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	Phe	
		930					935					940					
20	att	gcc	ctc	atg	acc	ttc	ggc	aac	tac	gtg	ctc	ttc	aat	ttg	ctg	gtc	2880
	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
	945					950					955					960	
	gcc	att	ctg	gtg	gag	ggc	ttc	cag	gcg	gag	gga	gat	gcc	aac	aag	tcc	2928
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Lys	Ser	
					965					970					975		
25	gaa	tca	gag	ccc	gat	ttc	ttc	tca	ccc	agc	ctg	gat	ggt	gat	ggg	gac	2976
	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp	
				980					985					990			
30	agg	aag	aag	tgc	ttg	gcc	ttg	gtg	tcc	ctg	gga	gag	cac	cgg	gag	ctg	3024
	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu	
			995				1000						1005				
35	cgg	aag	agc	ctg	ctg	cgg	cct	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro	
		1010				1015					1020						
40	atg	tgc	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	gcg	ctg	ggc	3120
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly	
	1025				1030					1035					1040		
	cct	gcg	tgc	cgc	cgc	acc	agc	agc	agc	ggg	tgc	gca	gag	cct	ggg	gcg	3168
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala	
				1045						1050					1055		
45	gcc	cac	gag	atg	aag	tca	cgg	ccc	agc	gcc	cgc	agc	tct	cgg	cac	agc	3216
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser	
				1060				1065						1070			
50	ccc	tgg	agc	gct	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	cgg	aac	3264
	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	Arg	Asn	
		1075					1080					1085					
55	agc	ctc	ggc	cgt	gca	ccc	agc	ctg	aag	cgg	aga	agc	cca	agt	gga	gag	3312
	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu	
		1090				1095					1100						
60	cgg	cgg	tcc	ctg	ttg	tgc	gga	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu	
	1105				1110					1115					1120		
	gag	agc	tca	gaa	gag	gag	cgg	gcc	agc	cct	gcg	ggc	agt	gac	cat	cgc	3408
	Glu	Ser	Ser	Glu	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg	
				1125				1130						1135			

	cac agg ggg tcc ctg gag cgg gag gcc aag agt tcc ttt gag ctg cca	3456
	His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp Leu Pro	
	1140 1145 1150	
5	gac aca ctg cag gtg cca ggg ctg cat cgc act gcc agt ggc cga ggg	3504
	Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly	
	1155 1160 1165	
10	tct gct tct gag cac cag gac tgc aat ggc aag tgc gct tca ggg cgc	3552
	Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg	
	1170 1175 1180	
15	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac	3600
	Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp	
	1185 1190 1195 1200	
20	gcc gat gac gag ggc aac ctg agc aaa ggg gaa cgg gtc cgc ggg tgg	3648
	Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp	
	1205 1210 1215	
25	atc cga gcc cga ctc cct gcc tgc tgc ctc gag cga gac tcc tgg tca	3696
	Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser	
	1220 1225 1230	
30	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctc ctg tgt cac cgg	3744
	Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg	
	1235 1240 1245	
35	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc	3792
	Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe	
	1250 1255 1260	
40	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac	3840
	Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His	
	1265 1270 1275 1280	
45	agc gct gaa cgc atc ttc ctg acc ctc tcc aat tac atc ttc acc gca	3888
	Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala	
	1285 1290 1295	
50	gtc ttt ctg gct gaa atg aca gtg aag gtg gtg gca ctg gcc tgg tgc	3936
	Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly Trp Cys	
	1300 1305 1310	
55	ttc ggg gag cag gcg tac ctg cgg agc agt tgg aac gtg ctg gac ggg	3984
	Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu Asp Gly	
	1315 1320 1325	
60	ctg ttg gtg ctc atc tcc gtc atc gac att ctg gtg tcc atg gtc tct	4032
	Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser	
	1330 1335 1340	
65	gac agc ggc acc aag atc ctg ggc atg ctg agg gtg ctg cgg ctg ctg	4080
	Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu	
	1345 1350 1355 1360	
70	cgg acc ctg cgc ccg ctc agg gtg atc agc cgg gcg cag ggc ctg aag	4128
	Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly Leu Lys	
	1365 1370 1375	
75	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa ccc atc gcc aac att	4176
	Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile	
	1380 1385 1390	

	gta gtc atc tgc tgt gcc ttc ttc atc att ttc ggc atc ttg ggg gtg	4224
	Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu Gly Val	
	1395 1400 1405	
5	cag ctg ttc aaa ggg aag ttt ttc gtg tgc cag ggc gag gat acc agg	4272
	Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp Thr Arg	
	1410 1415 1420	
10	aac atc acc aat aaa tgc gac tgt gcc gag gcc agt tac cgg tgg gtc	4320
	Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg Trp Val	
	1425 1430 1435 1440	
15	cgg cac aag tac aac ttt gac aac ctt ggc cag gcc ctg atg tcc ctg	4368
	Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu	
	1445 1450 1455	
20	ttc gtt ttg gcc tcc aag gat ggt tgg gtg gac atc atg tac gat ggg	4416
	Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr Asp Gly	
	1460 1465 1470	
25	ctg gat gct gtg ggc gtg gac cag cag ccc atc atg aac cac aac ccc	4464
	Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His Asn Pro	
	1475 1480 1485	
30	tgg atg ctg ctg tac ttc atc tgc ttc ctg ctg att gtg gcc ttc ttt	4512
	Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala Phe Phe	
	1490 1495 1500	
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30	tct gag tca gag cct gat ttc ttt tcc agt gtg gat ggt gat ggg Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Val Asp Gly Asp Gly 980 985 990			2976
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55	gct gcc cac cat gag atg aaa tgt ccg cca agt gcc cgc agc tcc ccg Ala Ala His His Glu Met Lys Cys Pro Pro Ser Ala Arg Ser Ser Pro 1060 1065 1070			3216
60	cac agt ccc tgg agt gcg gca agc agc tgg acc agc agg cgc tcc agc His Ser Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser 1075 1080 1085			3264
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80	gtc ccc cta gga cca gac ctg ctg act gtg agg aag tct ggt gtc agc Val Pro Leu Gly Pro Asp Leu Leu Thr Val Arg Lys Ser Gly Val Ser 1905 1910 1915	5760		

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10	act gct gag aga tcc cta gga cac agg ggc tgg ggg ctc ccc aaa gcc Thr Ala Glu Arg Ser Leu Gly His Arg Gly Trp Gly Leu Pro Lys Ala	1925 1940	1930 1945	1935 1950	5856
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65	gaa ccc ctg ttc cca cgg gac ctg aag aag tgc tac agt gta gag acc Glu Pro Leu Phe Pro Arg Asp Leu Lys Lys Cys Tyr Ser Val Glu Thr	2115 2120	2125	6384	
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2165 2170 2175

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 2180 2185 2190

10 ccg gag agc cag ggc tct cgg ccc cca tgc agt cct ggt gtc tgc ctc 6624
 Pro Glu Ser Gln Gly Ser Arg Pro Pro Cys Ser Pro Gly Val Cys Leu
 2195 2200 2205

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 Arg Arg Arg Ala Pro Ala Ser Asp Ser Lys Asp Pro Ser Val Ser Ser
 2210 2215 2220

15 ccc ctt gac agc acg gct gcc tca ccc tcc cca aag aaa gac acg ctg 6720
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 Arg Ser Phe Thr Gln Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Gln
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 Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
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 Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
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 Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
 65 70 75 80

60 ccg tgg ttc gag cga gtc agt atg ctg gtc att ctt ctc aac tgt gtg 288
 Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val
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act ctg ggt atg ttc agg ccg tgt gag gac att gcc tgt gac tcc cag 336
 Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
 100 105 110

60 cgc tgc cgg atc ctg cag gcc ttc gat gac ttc atc ttt gcc ttc ttt 384
 Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe
 115 120 125

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	Phe	Asp	Asn	Ile	Gly	Tyr	Ala	Trp	Ile	Ala	Ile	Phe	Gln	Val	Ile	Thr	
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	Leu	Glu	Gly	Trp	Val	Asp	Ile	Met	Tyr	Phe	Val	Met	Asp	Ala	His	Ser	
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	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe	
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	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys	
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	515 520 525	
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	Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Thr Pro Ser Gly	
	530 535 540	
55	ggc cct ccg agg ggt gcg gag tct gta cac agc ttc tac cat gct gac	1680
	Gly Pro Pro Arg Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp	
	545 550 555 560	
60	tgc cac ttg gag cca gtc cgt tgc cag gca ccc cct ccc aga tgc cca	1728
	Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Cys Pro	
	565 570 575	
65	tcg gag gca tct ggt agg act gtg ggt agt ggg aag gtg tac ccc act	1776
	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr	
	580 585 590	
70	gtg cat acc agc cct cca cca gag ata ctg aag gat aaa gca cta gtg	1824
	Val His Thr Ser Pro Pro Pro Glu Ile Leu Lys Asp Lys Ala Leu Val	
	595 600 605	
75	gag gtg gcc ccc agc cct ggg ccc ccc acc ctc acc agc ttc aac atc	1872
	Glu Val Ala Pro Ser Pro Gly Pro Pro Thr Leu Thr Ser Phe Asn Ile	
	610 615 620	
80	cca cct ggg ccc ttc agc tcc atg cac aag ctc ctg gag aca cag agt	1920
	Pro Pro Gly Pro Phe Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser	
	625 630 635 640	

	acg gga gcc tgc cat agc tcc tgc aaa atc tcc agc cct tgc tcc aag	1968
	Thr Gly Ala Cys His Ser Ser Cys Lys Ile Ser Ser Pro Cys Ser Lys	
	645 650 655	
5	gca gac agt gga gcc tgc ggg ccg gac agt tgt ccc tac tgt gcc cgg	2016
	Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg	
	660 665 670	
10	aca gga gca gga gag cca gag tcc gct gac cat gtc atg cct gac tca	2064
	Thr Gly Ala Gly Glu Pro Glu Ser Ala Asp His Val Met Pro Asp Ser	
	675 680 685	
15	gac agc gag gct gtg tat gag ttc aca cag gac gct cag cac agt gac	2112
	Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp	
	690 695 700	
20	ctc cgg gat ccc cac agc cgg cgg cga cag cgg agc ctg ggc cca gat	2160
	Leu Arg Asp Pro His Ser Arg Arg Arg Gln Arg Ser Leu Gly Pro Asp	
	705 710 715 720	
25	gca gag cct agt tct gtg ctg gct ttc tgg agg ctg atc tgt gac aca	2208
	Ala Glu Pro Ser Ser Val Leu Ala Phe Trp Arg Leu Ile Cys Asp Thr	
	725 730 735	
30	ttc cgg aag atc gta gat agc aaa tac ttt ggc cgg gga atc atg atc	2256
	Phe Arg Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile	
	740 745 750	
35	gcc atc ctg gtc aat aca ctc agc atg ggc atc gag tac cac gag cag	2304
	Ala Ile Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln	
	755 760 765	
40	ccc gag gag ctc acc aac gcc ctg gaa atc agc aac atc gtc ttc acc	2352
	Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr	
	770 775 780	
45	agc ctc ttc gcc ttg gag atg ctg ctg aaa ctg ctt gtc tac ggt ccc	2400
	Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro	
	785 790 795 800	
50	ttt ggc tac att aag aat ccc tac aac atc ttt gat ggt gtc att gtg	2448
	Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val	
	805 810 815	
55	gtc atc agt gtg tgg gag att gtg ggc cag cag gga ggt ggc ctg tcg	2496
	Val Ile Ser Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser	
	820 825 830	
60	gtg ctg cgg acc ttc cgc ctg atg cgg gtg ctg aag ctg gtg cgc ttc	2544
	Val Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe	
	835 840 845	
65	ctg ccg gcc ctg cag cgc cag ctc gtg gtg ctc atg aag acc atg gac	2592
	Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp	
	850 855 860	
70	aac gtg gcc acc ttc tgc atg ctc ctc atg ctg ttc atc ttc atc ttc	2640
	Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe	
	865 870 875 880	
75	agc atc ctg ggc atg cat ctc ttc ggt tgc aag ttc gca tct gaa cgg	2688
	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg	
	885 890 895	

	gat	ggg	gac	acg	ttg	cca	gac	cgg	aag	aat	ttc	gac	tcc	ctg	ctc	tgg	2736
	Asp	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	
				900					905					910			
5	gcc	atc	gtc	act	gtc	ttt	cag	att	ctg	act	cag	gaa	gac	tgg	aat	aaa	2784
	Ala	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	
			915					920					925				
10	gtc	ctc	tac	aac	ggc	atg	gcc	tcc	aca	tcg	tct	tgg	gct	gct	ctt	tac	2832
	Val	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	
			930				935					940					
15	ttc	atc	gcc	ctc	atg	act	ttt	ggc	aac	tat	gtg	ctc	ttt	aac	ctg	ctg	2880
	Phe	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	
	945					950					955					960	
20	gtg	gcc	att	ctt	gtg	gaa	gga	ttc	cag	gca	gag	gga	gat	gcc	acc	aag	2928
	Val	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Thr	Lys	
					965					970					975		
25	tct	gag	tca	gag	cct	gat	ttc	ttt	tcg	ccc	agt	gtg	gat	ggg	gat	ggg	2976
	Ser	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Val	Asp	Gly	Asp	Gly	
				980					985					990			
30	gac	aga	aag	aag	cgc	ttg	gcc	ctg	gtg	gct	ttg	gga	gaa	cac	gcg	gaa	3024
	Asp	Arg	Lys	Lys	Arg	Leu	Ala	Leu	Val	Ala	Leu	Gly	Glu	His	Ala	Glu	
			995					1000					1005				
35	cta	cga	aag	agc	ctt	ttg	cca	ccc	ctc	atc	atc	cat	acg	gct	gcg	aca	3072
	Leu	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	
		1010					1015					1020					
40	cca	atg	tca	cac	ccc	aag	agc	tcc	agc	aca	ggt	gtg	ggg	gaa	gca	ctg	3120
	Pro	Met	Ser	His	Pro	Lys	Ser	Ser	Ser	Thr	Gly	Val	Gly	Glu	Ala	Leu	
		1025				1030					1035					1040	
45	ggc	tct	ggc	tct	cga	cgt	acc	agt	agc	agt	ggg	tcc	gct	gag	cct	gga	3168
	Gly	Ser	Gly	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	
					1045					1050					1055		
50	gct	gcc	cac	cat	gag	atg	aaa	tgt	ccg	cca	agt	gcc	cgc	agc	tcc	ccg	3216
	Ala	Ala	His	His	Glu	Met	Lys	Cys	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	
				1060				1065					1070				
55	cac	agt	ccc	tgg	agt	gcg	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	3264
	His	Ser	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	
			1075				1080					1085					
60	agg	aac	agc	ctg	ggc	cgg	gcc	ccc	agc	cta	aag	cgg	agg	agc	ccg	agc	3312
	Arg	Asn	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	
		1090					1095					1100					
65	ggg	gag	cgg	agg	tcc	ctg	ctg	tct	gga	gag	ggc	cag	gag	agt	cag	gat	3360
	Gly	Glu	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	
		1105				1110					1115					1120	
70	gag	gag	gaa	agt	tca	gaa	gag	gac	cgg	gcc	agc	cca	gca	ggc	agt	gac	3408
	Glu	Glu	Glu	Ser	Ser	Glu	Glu	Asp	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	
					1125					1130					1135		
75	cat	cgc	cac	agg	ggg	tcc	ttg	gaa	cgt	gag	gcc	aag	agt	tcc	ttt	gac	3456
	His	Arg	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	
					1140				1145					1150			

	ctg cct gac act ctg cag gtg cgg ggg ctg cac cgc aca gcc agc ggc	3504
	Leu Pro Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly	
	1155 1160 1165	
5	egg agc tct gcc tct gag cac caa gac tgt aat ggc aag tgg gct tca	3552
	Arg Ser Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser	
	1170 1175 1180	
10	ggg cgt ttg gcc cgc acc ctg agg act gat gac ccc caa ctg gat ggg	3600
	Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly	
	1185 1190 1195 1200	
15	gat gat gac aat gat gag gga aat ctg agc aaa ggg gaa cgc ata caa	3648
	Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Ile Gln	
	1205 1210 1215	
20	gcc tgg gtc aga tcc cgg ctt cct gcc tgt tgc cga gag cga gat tcc	3696
	Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser	
	1220 1225 1230	
	tgg tgg gcc tat atc ttt cct cct cag tca agg ttt cgt ctc ctg tgt	3744
	Trp Ser Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys	
	1235 1240 1245	
25	cac cgg atc atc acc cac aag atg ttt gac cat gtg gtc ctc gtc atc	3792
	His Arg Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile	
	1250 1255 1260	
30	atc ttc ctc aac tgt atc acc atc gct atg gag cgc ccc aaa att gac	3840
	Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp	
	1265 1270 1275 1280	
35	ccc cac agc gct gag cgc atc ttc ctg acc ctc tcc aac tac atc ttc	3888
	Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe	
	1285 1290 1295	
40	acg gca gtc ttt cta gct gaa atg aca gtg aag gtg gtg gca ctg ggc	3936
	Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly	
	1300 1305 1310	
	tgg tgc ttt ggg gag cag gcc tac ctg cgc agc agc tgg aat gtg ctg	3984
	Trp Cys Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu	
	1315 1320 1325	
45	gac ggc ttg ctg gtg ctc atc tcc gtc atc gac atc ctg gtc tcc atg	4032
	Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met	
	1330 1335 1340	
50	gtc tcc gac agc ggc acc aag atc ctt ggc atg ctg agg gtg ctg cgg	4080
	Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg	
	1345 1350 1355 1360	
55	ctg ctg cgg acc ctg cgt cca ctc agg gtc atc agc cgg gcc cag gga	4128
	Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly	
	1365 1370 1375	
	ctg aag ctg gtg gta gag act ctg atg tca tcc ctc aaa ccc att ggc	4176
	Leu Lys Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly	
60	1380 1385 1390	
	aac att gtg gtc att tgc tgc gcc ttc ttc atc att ttt gga att ctc	4224
	Asn Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu	
	1395 1400 1405	

	ggg gtg cag ctc ttc aaa ggg aag ttc ttc gtg tgt cag ggt gag gac	4272
	Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp	
	1410 1415 1420	
5	acc agg aac atc act aac aaa tcc gac tgc gct gag gcc agc tac cga	4320
	Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg	
	1425 1430 1435 1440	
10	tgg gtc cgg cac aag tac aac ttt gac aac ctg gcc cag gct ctg atg	4368
	Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met	
	1445 1450 1455	
15	tcc ctg ttt gtg ctg gcc tcc aag gat ggt tgg gtt gac atc atg tat	4416
	Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr	
	1460 1465 1470	
20	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc atc atg aac cac	4464
	Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His	
	1475 1480 1485	
25	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctc ctc atc gtg gcc	4512
	Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala	
	1490 1495 1500	
	ttc ttt gtc ctg aac atg ttt gtg ggc gtg gtg gtg gag aac ttc cat	4560
	Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His	
	1505 1510 1515 1520	
30	aag tgc aga cag cac cag gag gag gag gag gcg agg cgg cgt gag gag	4608
	Lys Cys Arg Gln His Gln Glu Glu Glu Glu Ala Arg Arg Arg Glu Glu	
	1525 1530 1535	
35	aag cga cta cgg agg ctg gag aaa aag aga agg aat cta atg ttg gac	4656
	Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Asn Leu Met Leu Asp	
	1540 1545 1550	
40	gat gta att gct tcc ggc agc tca gcc agc gct gcg tca gaa gcc cag	4704
	Asp Val Ile Ala Ser Gly Ser Ser Ala Ser Ala Ala Ser Glu Ala Gln	
	1555 1560 1565	
45	tgc aag ccc tac tac tct gac tac tcg aga ttc cgg ctc ctt gtc cac	4752
	Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe Arg Leu Leu Val His	
	1570 1575 1580	
	cac ctg tgt acc agc cac tac ctg gac ctc ttc atc act ggt gtc atc	4800
	His Leu Cys Thr Ser His Tyr Leu Asp Leu Phe Ile Thr Gly Val Ile	
	1585 1590 1595 1600	
50	ggg ctg aac gtg gtc act atg gcc atg gaa cat tac cag cag ccc cag	4848
	Gly Leu Asn Val Val Thr Met Ala Met Glu His Tyr Gln Gln Pro Gln	
	1605 1610 1615	
55	atc ctg gac gag gct ctg aag atc tgc aat tac atc ttt acc gtc atc	4896
	Ile Leu Asp Glu Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile	
	1620 1625 1630	
60	ttt gtc ttt gag tca gtt ttc aaa ctt gtg gcc ttt ggc ttc cgc cgt	4944
	Phe Val Phe Glu Ser Val Phe Lys Leu Val Ala Phe Gly Phe Arg Arg	
	1635 1640 1645	
	ttc ttc cag gac agg tgg aac cag ctg gac ctg gct att gtg ctt ctg	4992
	Phe Phe Gln Asp Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu	
	1650 1655 1660	

	tec atc atg ggc atc aca ctg gag gag att gag gtc aat ctg tct ctg	5040
	Ser Ile Met Gly Ile Thr Leu Glu Glu Ile Glu Val Asn Leu Ser Leu	
	1665 1670 1675 1680	
5	ccc atc aac ccc acc atc atc cgt atc atg agg gtg ctc cgc att gct	5088
	Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala	
	1685 1690 1695	
10	cga gtt ctg aag ctg ttg aag atg gct gtg ggc atg cgg gca ctg ctg	5136
	Arg Val Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg Ala Leu Leu	
	1700 1705 1710	
15	cac acg gtg atg cag gcc ctg ccc cag gtg ggg aac ctg gga ctt ctc	5184
	His Thr Val Met Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu	
	1715 1720 1725	
20	ttc atg tta ttg ttt ttc atc ttt gca gct ctg ggc gtg gag ctc ttc	5232
	Phe Met Leu Leu Phe Phe Ile Phe Ala Ala Leu Gly Val Glu Leu Phe	
	1730 1735 1740	
25	gga gac ctg gag tgt gat gag aca cac cct tgt gag ggc ttg ggt cgg	5280
	Gly Asp Leu Glu Cys Asp Glu Thr His Pro Cys Glu Gly Leu Gly Arg	
	1745 1750 1755 1760	
	cat gcc acc ttt agg aac ttt ggt atg gcc ttt ctg acc ctc ttc cga	5328
	His Ala Thr Phe Arg Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg	
	1765 1770 1775	
30	gtc tcc act ggt gac aac tgg aat ggt att atg aag gac acc ctc cgg	5376
	Val Ser Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg	
	1780 1785 1790	
35	gac tgt gac cag gag tcc acc tgc tac aac act gtc atc tcc cct atc	5424
	Asp Cys Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val Ile Ser Pro Ile	
	1795 1800 1805	
40	tac ttt gtg tcc ttc gtg ctg acg gcc cag ttt gtg ctg gtc aac gtg	5472
	Tyr Phe Val Ser Phe Val Leu Thr Ala Gln Phe Val Leu Val Asn Val	
	1810 1815 1820	
45	gtc ata gct gtg ctg atg aag cac ctg gaa gaa agc aac aaa gag gcc	5520
	Val Ile Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys Glu Ala	
	1825 1830 1835 1840	
	aag gag gag gcc gag ctc gag gcc gag ctg gag ctg gag atg aag acg	5568
	Lys Glu Glu Ala Glu Leu Glu Ala Glu Leu Glu Leu Glu Met Lys Thr	
	1845 1850 1855	
50	ctc agc ccg cag ccc cac tcc ccg ctg ggc agc ccc ttc ctc tgg ccc	5616
	Leu Ser Pro Gln Pro His Ser Pro Leu Gly Ser Pro Phe Leu Trp Pro	
	1860 1865 1870	
55	ggg gtg gag ggt gtc aac agt act gac agc cct aag cct ggg gct cca	5664
	Gly Val Glu Gly Val Asn Ser Thr Asp Ser Pro Lys Pro Gly Ala Pro	
	1875 1880 1885	
60	cac acc act gcc cac att gga gca gcc tct ggc ttc tcc ctt gag cac	5712
	His Thr Thr Ala His Ile Gly Ala Ala Ser Gly Phe Ser Leu Glu His	
	1890 1895 1900	
	ccc acg atg gta ccc cac ccc gag gag gtg cca gtc ccc cta gga cca	5760
	Pro Thr Met Val Pro His Pro Glu Glu Val Pro Val Pro Leu Gly Pro	
	1905 1910 1915 1920	

	gac	ctg	ctg	act	gtg	agg	aag	tct	ggt	gtc	agc	cgg	acg	cac	tct	ctg	5808
	Asp	Leu	Leu	Thr	Val	Arg	Lys	Ser	Gly	Val	Ser	Arg	Thr	His	Ser	Leu	
				1925					1930							1935	
5	ccc	aat	gac	agc	tac	atg	tgc	cgc	aat	ggg	agc	act	gct	gag	aga	tcc	5856
	Pro	Asn	Asp	Ser	Tyr	Met	Cys	Arg	Asn	Gly	Ser	Thr	Ala	Glu	Arg	Ser	
				1940					1945							1950	
10	cta	gga	cac	agg	ggc	tgg	ggg	ctc	ccc	aaa	gcc	cag	tca	ggc	tcc	atc	5904
	Leu	Gly	His	Arg	Gly	Trp	Gly	Leu	Pro	Lys	Ala	Gln	Ser	Gly	Ser	Ile	
				1955					1960							1965	
15	ttg	tcc	gtt	cac	tcc	caa	cca	gca	gac	acc	agc	tgc	atc	cta	cag	ctt	5952
	Leu	Ser	Val	His	Ser	Gln	Pro	Ala	Asp	Thr	Ser	Cys	Ile	Leu	Gln	Leu	
				1970					1975							1980	
20	ccc	aaa	gat	gtg	cac	tac	ctg	ctc	cag	cct	cat	ggg	gct	ccc	acc	tgg	6000
	Pro	Lys	Asp	Val	His	Tyr	Leu	Leu	Gln	Pro	His	Gly	Ala	Pro	Thr	Trp	
				1985					1990							2000	
25	ggc	gcc	atc	cct	aaa	cta	ccc	cca	cct	ggc	cgc	tcc	cct	ctg	gct	cag	6048
	Gly	Ala	Ile	Pro	Lys	Leu	Pro	Pro	Pro	Gly	Arg	Ser	Pro	Leu	Ala	Gln	
					2005					2010						2015	
30	agg	cct	ctc	agg	cgc	cag	gca	gca	ata	agg	act	gac	tcc	ctg	gat	gtg	6096
	Arg	Pro	Leu	Arg	Arg	Gln	Ala	Ala	Ile	Arg	Thr	Asp	Ser	Leu	Asp	Val	
				2020						2025						2030	
35	cag	ggc	ctg	ggt	agc	cgg	gaa	gac	ctg	ttg	tca	gag	gtg	agt	ggg	ccc	6144
	Gln	Gly	Leu	Gly	Ser	Arg	Glu	Asp	Leu	Leu	Ser	Glu	Val	Ser	Gly	Pro	
				2035					2040							2045	
40	tcc	tgc	cct	ctg	acc	cgg	tcc	tca	tcc	ttc	tgg	ggc	ggg	tgc	agc	atc	6192
	Ser	Cys	Pro	Leu	Thr	Arg	Ser	Ser	Ser	Phe	Trp	Gly	Gly	Ser	Ser	Ile	
				2050					2055							2060	
45	cag	gtg	cag	cag	cgt	tcc	ggc	atc	cag	agc	aaa	gtc	tcc	aag	cac	atc	6240
	Gln	Val	Gln	Gln	Arg	Ser	Gly	Ile	Gln	Ser	Lys	Val	Ser	Lys	His	Ile	
									2065							2080	
50	cgc	ctg	cca	ggc	cct	tgc	cca	ggc	ctg	gaa	ccc	agc	tgg	ggc	aag	gac	6288
	Arg	Leu	Pro	Ala	Pro	Cys	Pro	Gly	Leu	Glu	Pro	Ser	Trp	Ala	Lys	Asp	
						2085				2090						2095	
55	cct	cca	gag	acc	aga	agc	agc	tta	gag	ctg	gac	acg	gag	ctg	agc	tgg	6336
	Pro	Pro	Glu	Thr	Arg	Ser	Ser	Leu	Glu	Leu	Asp	Thr	Glu	Leu	Ser	Trp	
						2100				2105						2110	
60	att	tca	gga	gac	ctc	ctt	ccc	agc	agc	cag	gaa	gaa	ccc	ctg	ttc	cca	6384
	Ile	Ser	Gly	Asp	Leu	Leu	Pro	Ser	Ser	Gln	Glu	Glu	Pro	Leu	Phe	Pro	
									2115							2125	
65	cgg	gac	ctg	aag	aag	tgc	tac	agt	gta	gag	acc	cag	agc	tgc	agg	cgc	6432
	Arg	Asp	Leu	Lys	Lys	Cys	Tyr	Ser	Val	Glu	Thr	Gln	Ser	Cys	Arg	Arg	
						2130										2140	
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 Lys Leu Ser Pro Pro Ser Ile Ser Ile Asp Pro Pro Glu Ser Gln Gly
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 Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val
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15	gca	gac	agt	gga	gcc	tgc	ggg	ccg	gac	agt	tgt	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660					665					670			
20	aca	gga	gca	gga	gag	cca	gag	tcc	gct	gac	cat	gtc	atg	cct	gac	tca	2064
	Thr	Gly	Ala	Gly	Glu	Pro	Glu	Ser	Ala	Asp	His	Val	Met	Pro	Asp	Ser	
				675				680					685				
25	gac	agc	gag	gct	gtg	tat	gag	ttc	aca	cag	gac	gct	cag	cac	agt	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
		690					695					700					
30	ctc	cgg	gat	ccc	cac	agc	cgg	cgg	cga	cag	cgg	agc	ctg	ggc	cca	gat	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	
	705					710					715					720	
35	gca	gag	cct	agt	tct	gtg	ctg	gct	ttc	tgg	agg	ctg	atc	tgt	gac	aca	2208
	Ala	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	
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40	ttc	cgg	aag	atc	gta	gat	agc	aaa	tac	ttt	ggc	cgg	gga	atc	atg	atc	2256
	Phe	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	
				740					745					750			
45	gcc	atc	ctg	gtc	aat	aca	ctc	agc	atg	ggc	atc	gag	tac	cac	gag	cag	2304
	Ala	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	
			755					760					765				
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	Pro	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	
		770					775					780					
55	agc	ctc	ttc	gcc	ttg	gag	atg	ctg	ctg	aaa	ctg	ctt	gtc	tac	ggc	ccc	2400
	Ser	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	
	785					790				795						800	
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	Phe	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	
					805					810					815		
65	gtc	atc	agt	gtg	tgg	gag	att	gtg	ggc	cag	cag	gga	ggc	ggc	ctg	tcg	2496
	Val	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	
				820					825				830				
70	gtg	ctg	cgg	acc	ttc	cgc	ctg	atg	cgg	gtg	ctg	aag	ctg	gtg	cgc	ttc	2544
	Val	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	
			835					840					845				
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	Leu	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	
		850					855					860					
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	Asn	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	
	865					870					875					880	
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10	gat	ggg	gac	acg	ttg	cca	gac	cgg	aag	aat	ttc	gac	tcc	ctg	ctc	tgg	2736
	Asp	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	
				900					905					910			
15	gcc	atc	gtc	act	gtc	ttt	cag	att	ctg	act	cag	gaa	gac	tgg	aat	aaa	2784
	Ala	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	
			915					920					925				
20	gtc	ctc	tac	aac	ggc	atg	gcc	tcc	aca	tcg	tct	tgg	gct	gct	ctt	tac	2832
	Val	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	
			930				935					940					
25	ttc	atc	gcc	ctc	atg	act	ttt	ggc	aac	tat	gtg	ctc	ttt	aac	ctg	ctg	2880
	Phe	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	
	945					950					955					960	
30	gtg	gcc	att	ctt	gtg	gaa	gga	ttc	cag	gca	gag	gga	gat	gcc	acc	aag	2928
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	Ser	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Val	Asp	Gly	Asp	Gly	
				980					985					990			
40	gac	aga	aag	aag	cgc	ttg	gcc	ctg	gtg	gct	ttg	gga	gaa	cac	gcg	gaa	3024
	Asp	Arg	Lys	Lys	Arg	Leu	Ala	Leu	Val	Ala	Leu	Gly	Glu	His	Ala	Glu	
			995					1000					1005				
45	cta	cga	aag	agc	ctt	ttg	cca	ccc	ctc	atc	atc	cat	acg	gct	gcg	aca	3072
	Leu	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	
		1010					1015					1020					
50	cca	atg	tca	cac	ccc	aag	agc	tcc	agc	aca	ggg	gtg	ggg	gaa	gca	ctg	3120
	Pro	Met	Ser	His	Pro	Lys	Ser	Ser	Ser	Thr	Gly	Val	Gly	Glu	Ala	Leu	
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55	ggc	tct	ggc	tct	cga	cgt	acc	agt	agc	agt	ggg	tcc	gct	gag	cct	gga	3168
	Gly	Ser	Gly	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	
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60	gct	gcc	cac	cat	gag	atg	aaa	tgt	ccg	cca	agt	gcc	cgc	agc	tcc	ccg	3216
	Ala	Ala	His	His	Glu	Met	Lys	Cys	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	
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	His	Ser	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	
			1075					1080					1085				
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	Arg	Asn	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	
		1090					1095					1100					
75	ggg	gag	cgg	agg	tcc	ctg	ctg	tct	gga	gag	ggc	cag	gag	agt	cag	gat	3360
	Gly	Glu	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	
	1105					1110					1115					1120	
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	Glu	Glu	Glu	Ser	Ser	Glu	Glu	Asp	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	
					1125					1130					1135		
5	cat	cgc	cac	agg	ggc	tcc	ttg	gaa	cgt	gag	gcc	aag	agt	tcc	ttt	gac	3456
	His	Arg	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	
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10	ctg	cct	gac	act	ctg	cag	gtg	ccg	ggg	ctg	cac	cgc	aca	gcc	agc	ggc	3504
	Leu	Pro	Asp	Thr	Leu	Gln	Val	Pro	Gly	Leu	His	Arg	Thr	Ala	Ser	Gly	
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15	cgg	agc	tct	gcc	tct	gag	cac	caa	gac	tgt	aat	ggc	aag	tgc	gct	tca	3552
	Arg	Ser	Ser	Ala	Ser	Glu	His	Gln	Asp	Cys	Asn	Gly	Lys	Ser	Ala	Ser	
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20	ggg	cgt	ttg	gcc	cgc	acc	ctg	agg	act	gat	gac	ccc	caa	ctg	gat	ggg	3600
	Gly	Arg	Leu	Ala	Arg	Thr	Leu	Arg	Thr	Asp	Asp	Pro	Gln	Leu	Asp	Gly	
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25	gat	gat	gac	aat	gat	gag	gga	aat	ctg	agc	aaa	ggg	gaa	cgc	ata	caa	3648
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	Ala	Trp	Val	Arg	Ser	Arg	Leu	Pro	Ala	Cys	Cys	Arg	Glu	Arg	Asp	Ser	
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35	tgg	tgc	gcc	tat	atc	ttt	cct	cct	cag	tca	agg	ttt	cgt	ctc	ctg	tgt	3744
	Trp	Ser	Ala	Tyr	Ile	Phe	Pro	Pro	Gln	Ser	Arg	Phe	Arg	Leu	Leu	Cys	
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	His	Arg	Ile	Ile	Thr	His	Lys	Met	Phe	Asp	His	Val	Val	Leu	Val	Ile	
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45	atc	ttc	ctc	aac	tgt	atc	acc	atc	gct	atg	gag	cgc	ccc	aaa	att	gac	3840
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55	acg	gca	gtc	ttt	cta	gct	gaa	atg	aca	gtg	aag	gtg	gtg	gca	ctg	ggc	3936
	Thr	Ala	Val	Phe	Leu	Ala	Glu	Met	Thr	Val	Lys	Val	Val	Ala	Leu	Gly	
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	Trp	Cys	Phe	Gly	Glu	Gln	Ala	Tyr	Leu	Arg	Ser	Ser	Trp	Asn	Val	Leu	
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	Asp	Gly	Leu	Leu	Val	Leu	Ile	Ser	Val	Ile	Asp	Ile	Leu	Val	Ser	Met	
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	Val	Ser	Asp	Ser	Gly	Thr	Lys	Ile	Leu	Gly	Met	Leu	Arg	Val	Leu	Arg	
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75	ctg	ctg	cgg	acc	ctg	cgt	cca	ctc	agg	gtc	atc	agc	cgg	gcc	cag	gga	4128
	Leu	Leu	Arg	Thr	Leu	Arg	Pro	Leu	Arg	Val	Ile	Ser	Arg	Ala	Gln	Gly	
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	Leu	Lys	Leu	Val	Val	Glu	Thr	Leu	Met	Ser	Ser	Leu	Lys	Pro	Ile	Gly	
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			1395					1400					1405				
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		1410					1415					1420					
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	1425					1430					1435					1440	
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	Trp	Val	Arg	His	Lys	Tyr	Asn	Phe	Asp	Asn	Leu	Gly	Gln	Ala	Leu	Met	
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25	tcc	ctg	ttt	gtg	ctg	gcc	tcc	aag	gat	ggc	tgg	gtt	gac	atc	atg	tat	4416
	Ser	Leu	Phe	Val	Leu	Ala	Ser	Lys	Asp	Gly	Trp	Val	Asp	Ile	Met	Tyr	
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	Asp	Gly	Leu	Asp	Ala	Val	Gly	Val	Asp	Gln	Gln	Pro	Ile	Met	Asn	His	
		1475					1480						1485				
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	Lys	Cys	Arg	Gln	His	Gln	Glu	Glu	Glu	Glu	Glu	Ala	Arg	Arg	Arg	Glu	
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	Lys	Arg	Leu	Arg	Arg	Leu	Glu	Lys	Lys	Arg	Arg	Lys	Ala	Gln	Cys	Lys	
			1540					1545					1550				
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	Pro	Tyr	Tyr	Ser	Asp	Tyr	Ser	Arg	Phe	Arg	Leu	Leu	Val	His	His	Leu	
		1555						1560					1565				
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	Cys	Thr	Ser	His	Tyr	Leu	Asp	Leu	Phe	Ile	Thr	Gly	Val	Ile	Gly	Leu	
		1570					1575					1580					
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	Asp	Glu	Ala	Leu	Lys	Ile	Cys	Asn	Tyr	Ile	Phe	Thr	Val	Ile	Phe	Val	
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	Phe	Glu	Ser	Val	Phe	Lys	Leu	Val	Ala	Phe	Gly	Phe	Arg	Arg	Phe	Phe	
				1620					1625					1630			
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			1635					1640					1645				
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		1650				1655					1660						
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15	ctg	aag	ctg	ttg	aag	atg	gct	gtg	ggc	atg	cgg	gca	ctg	ctg	cac	acg	5088
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			1700						1705					1710			
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		1730				1735					1740						
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			1780					1785					1790				
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	Val	Ser	Phe	Val	Leu	Thr	Ala	Gln	Phe	Val	Leu	Val	Asn	Val	Val	Ile	
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		1810				1815					1820						
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	Glu	Ala	Glu	Leu	Glu	Ala	Glu	Leu	Glu	Leu	Glu	Met	Lys	Thr	Leu	Ser	
	1825				1830				1835						1840		
65	ccg	cag	ccc	cac	tcc	ccg	ctg	ggc	agc	ccc	ttc	ctc	tgg	ccc	ggg	gtg	5568
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	Thr	Ala	His	Ile	Gly	Ala	Ala	Ser	Gly	Phe	Ser	Leu	Glu	His	Pro	Thr	
		1875				1880						1885					
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	Leu	Thr	Val	Arg	Lys	Ser	Gly	Val	Ser	Arg	Thr	His	Ser	Leu	Pro	Asn	
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	Asp	Ser	Tyr	Met	Cys	Arg	Asn	Gly	Ser	Thr	Ala	Glu	Arg	Ser	Leu	Gly	
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	His	Arg	Gly	Trp	Gly	Leu	Pro	Lys	Ala	Gln	Ser	Gly	Ser	Ile	Leu	Ser	
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	Ile	Pro	Lys	Leu	Pro	Pro	Pro	Gly	Arg	Ser	Pro	Leu	Ala	Gln	Arg	Pro	
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	Leu	Arg	Arg	Gln	Ala	Ala	Ile	Arg	Thr	Asp	Ser	Leu	Asp	Val	Gln	Gly	
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	Gly	Asp	Leu	Leu	Pro	Ser	Ser	Gln	Glu	Glu	Pro	Leu	Phe	Pro	Arg	Asp	
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	Leu	Lys	Lys	Cys	Tyr	Ser	Val	Glu	Thr	Gln	Ser	Cys	Arg	Arg	Arg	Pro	
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	Leu Asp Ser Gly Ser Gln Pro Arg Leu Cys Pro Ser Pro Ser Ser Leu	
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5	ggg ggc caa cct ctt ggg ggt cct ggg agc cgg cct aag aaa aaa ctc Gly Gly Gln Pro Leu Gly Gly Pro Gly Ser Arg Pro Lys Lys Lys Leu	6528
	2165 2170 2175	
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	2180 2185 2190	
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	2195 2200 2205	
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	20 25 30	
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	35 40 45	
	ccc tcc gag agc ccg gcg gcc gag cgc tgc gcg gag ctg ggt gcc gac Pro Ser Glu Ser Pro Ala Ala Glu Arg Cys Ala Glu Leu Gly Ala Asp	192
	50 55 60	
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	65 70 75 80	
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	85 90 95	
	tgc aac cca tgg ttc gag cac gtg agc atg ctg gta atc atg ctc aac Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu Asn	336

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	Ser	Glu	Arg	Cys	Asn	Ile	Leu	Glu	Ala	Phe	Asp	Ala	Phe	Ile	Phe	Ala						
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		210					215					220										
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	Tyr	Thr	Gln	Pro	Gln	Ala	Glu	Gly	Val	Gly	Ala	Ala	Arg	Asn	Ala	Cys						
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	Leu Pro Ser Ser Cys Ala Gln Leu	Pro Arg Pro Cys Leu Pro Pro Arg							
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70	gct cac cat tcc tgg atg cag ccc	cca gcc tcc cag act ctc ggc gtg	3312						
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75	gca gca gca gct ccg ggg acc cgc	cac tgg gag acc aga agc ctc cgg	3360						
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	1635	1640	1645	
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	Arg	Glu	Gln	Arg	Ala	Arg	His	Leu	Ser	Asn	Asp	Ser	Thr	Leu	Ala	Ser	
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	Gln	Gly	Pro	Gly	His	Arg	Gln	Arg	Arg	Ala	Gly	Arg	His	Thr	Ala	Ser	
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	Val	His	His	Leu	Val	Tyr	His	His	His	His	His	His	His	His	His	Tyr	
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	His	Phe	Ser	His	Gly	Ser	Pro	Arg	Arg	Pro	Gly	Pro	Glu	Pro	Gly	Ala	
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	Arg His Arg Gly His Gly Pro Leu Ser Leu Asn Ser Pro Asp Pro Tyr	
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	Val Pro His Pro Asp Leu Ala Pro Ile Ala Phe Phe Cys Leu Arg Gln	
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	Tyr Met Phe Thr Thr Val Phe Val Leu Glu Ala Val Leu Lys Leu Val	
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 Pro Pro Gly Leu Glu Glu Pro Leu Glu Gly Thr Asn Pro Asp Val Pro
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75	tat	gag	gag	atc	ttc	caa	tat	gtc	tgt	cac	atc	ctt	cgc	aaa	gcc	aag	1344
	Tyr	Glu	Glu	Ile	Phe	Gln	Tyr	Val	Cys	His	Ile	Leu	Arg	Lys	Ala	Lys	
					435			440					445				
80	cgc	cgt	gcc	cta	ggc	ctc	tac	cag	gcc	ctg	cag	aac	cgg	cgc	cag	gcc	1392

	Arg	Arg	Ala	Leu	Gly	Leu	Tyr	Gln	Ala	Leu	Gln	Asn	Arg	Arg	Gln	Ala	
	450						455					460					
5	atg	ggc	ccg	ggg	aca	cca	gcc	cct	gcc	aag	cct	ggg	ccc	cat	gcc	aag	1440
	Met	Gly	Pro	Gly	Thr	Pro	Ala	Pro	Ala	Lys	Pro	Gly	Pro	His	Ala	Lys	
	465					470					475					480	
10	gag	ccc	agc	cac	tgc	aag	ctg	tgc	cca	cga	cac	agc	ccc	ctg	gac	ccc	1489
	Glu	Pro	Ser	His	Cys	Lys	Leu	Cys	Pro	Arg	His	Ser	Pro	Leu	Asp	Pro	
					485					490					495		
15	act	ccc	cac	aca	ctg	gtg	cag	ccc	atc	tct	gcc	att	ctg	gcc	tct	gac	1536
	Thr	Pro	His	Thr	Leu	Val	Gln	Pro	Ile	Ser	Ala	Ile	Leu	Ala	Ser	Asp	
				500					505					510			
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	Pro	Ser	Ser	Cys	Pro	His	Cys	Gln	His	Glu	Ala	Gly	Arg	Arg	Pro	Ser	
				515				520					525				
25	ggc	ctg	ggc	agc	act	gac	tca	ggc	cag	gaa	ggc	tca	ggt	tct	ggt	ggc	1632
	Gly	Leu	Gly	Ser	Thr	Asp	Ser	Gly	Gln	Glu	Gly	Ser	Gly	Ser	Gly	Gly	
		530					535					540					
30	tct	gca	gag	gcc	gaa	gcc	aat	ggg	gat	gga	ctc	cag	agc	agt	gag	gat	1680
	Ser	Ala	Glu	Ala	Glu	Ala	Asn	Gly	Asp	Gly	Leu	Gln	Ser	Ser	Glu	Asp	
	545					550					555					560	
35	ggg	gtc	tcc	tcg	gac	ctg	ggg	aag	gag	gag	gaa	cag	gag	gac	ggg	gca	1728
	Gly	Val	Ser	Ser	Asp	Leu	Gly	Lys	Glu	Glu	Glu	Gln	Glu	Asp	Gly	Ala	
					565					570					575		
40	ggc	cga	ctg	tgt	ggg	gat	gtg	tgg	cgc	gag	aca	cga	aaa	aag	ctg	cgg	1776
	Ala	Arg	Leu	Cys	Gly	Asp	Val	Trp	Arg	Glu	Thr	Arg	Lys	Lys	Leu	Arg	
				580					585					590			
45	ggc	atc	gtg	gac	agc	aag	tac	ttc	aac	aga	ggt	atc	atg	atg	gct	atc	1824
	Gly	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Asn	Arg	Gly	Ile	Met	Met	Ala	Ile	
			595				600						605				
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	Leu	Val	Asn	Thr	Val	Ser	Met	Gly	Ile	Glu	His	His	Glu	Gln	Pro	Glu	
		610					615					620					
55	gag	ctg	acc	aac	atc	ctg	gag	atc	tgc	aat	gtg	gtc	ttc	acc	agt	atg	1920
	Glu	Leu	Thr	Asn	Ile	Leu	Glu	Ile	Cys	Asn	Val	Val	Phe	Thr	Ser	Met	
	625					630					635					640	
60	ttt	gcc	ctg	gag	atg	atc	ctg	aaa	ctg	gcc	gcc	ttt	ggg	ctc	ttc	gac	1968
	Phe	Ala	Leu	Glu	Met	Ile	Leu	Lys	Leu	Ala	Ala	Phe	Gly	Leu	Phe	Asp	
					645					650					655		
65	tac	ctg	cgg	aac	cct	tac	aac	atc	ttt	gac	agc	atc	atc	gtc	atc	atc	2016
	Tyr	Leu	Arg	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Ser	Ile	Ile	Val	Ile	Ile	
				660					665					670			
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	Ser	Ile	Trp	Glu	Ile	Val	Gly	Gln	Ala	Asp	Gly	Gly	Leu	Ser	Val	Leu	
			675					680					685				
75	cgc	acc	ttc	cgg	ttg	ctg	cgg	gtg	ctg	aag	ctg	gtg	cgc	ttc	atg	ccg	2112
	Arg	Thr	Phe	Arg	Leu	Leu	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Met	Pro	
		690					695					700					
80	gcg	ctg	cgg	cgc	cag	ctc	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	gtg	2160

	Ala	Leu	Arg	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	Val	
	705					710					715					720	
5	gcc	acc	ttc	tgc	atg	cta	ctc	atg	ctg	ttc	atc	ttc	atc	ttc	agc	atc	2208
	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	Ile	
					725					730					735		
10	ctt	ggg	atg	cat	atc	ttt	ggc	tgc	aaa	ttc	agc	ctc	cgc	acg	gac	acg	2256
	Leu	Gly	Met	His	Ile	Phe	Gly	Cys	Lys	Phe	Ser	Leu	Arg	Thr	Asp	Thr	
				740					745					750			
15	gga	gac	acc	gtt	cct	gac	agg	aag	aac	ttc	gat	tcc	tta	ctg	tgg	gcc	2304
	Gly	Asp	Thr	Val	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
			755					760					765				
20	atc	gtc	aca	gtg	ttc	cag	atc	ctc	act	cag	gag	gac	tgg	aac	gtt	gtc	2352
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Val	Val	
		770				775						780					
25	ctg	tac	aat	ggc	atg	gcc	tcc	acc	acc	ccc	tgg	gcc	tcc	ctc	tat	ttt	2400
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Thr	Pro	Trp	Ala	Ser	Leu	Tyr	Phe	
	785					790					795					800	
30	gtt	gcc	ctc	atg	acc	ttt	ggc	aac	tac	gtt	ctc	ttc	aat	ctc	ctg	gtg	2448
	Val	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
					805					810					815		
35	gct	atc	ctg	gta	gag	ggt	ttc	cag	gct	gag	ggt	gat	gct	aat	cgt	tcc	2496
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Arg	Ser	
				820					825					830			
40	tgc	tct	gat	gag	gac	cag	agc	tca	tcc	aat	ttg	gag	gag	ttt	gac	aag	2544
	Cys	Ser	Asp	Glu	Asp	Gln	Ser	Ser	Ser	Asn	Leu	Glu	Glu	Phe	Asp	Lys	
			835					840					845				
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	Leu	Pro	Glu	Gly	Leu	Asp	Asn	Ser	Arg	Asp	Leu	Lys	Leu	Cys	Pro	Ile	
		850					855					860					
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	Pro	Met	Thr	Pro	Asn	Gly	His	Leu	Asp	Pro	Ser	Leu	Pro	Leu	Gly	Ala	
	865					870					875					880	
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	His	Leu	Gly	Pro	Ala	Gly	Thr	Met	Gly	Thr	Ala	Pro	Arg	Leu	Ser	Leu	
				885						890					895		
60	cag	cca	gac	ccg	gta	ctg	gtg	gcc	cta	gac	tct	cgg	aaa	agc	agt	gtc	2736
	Gln	Pro	Asp	Pro	Val	Leu	Val	Ala	Leu	Asp	Ser	Arg	Lys	Ser	Ser	Val	
				900					905					910			
65	atg	tcc	ctg	ggc	agg	atg	agc	tat	gat	cag	cga	tcc	ttg	tcc	agc	tcc	2784
	Met	Ser	Leu	Gly	Arg	Met	Ser	Tyr	Asp	Gln	Arg	Ser	Leu	Ser	Ser	Ser	
			915					920					925				
70	cgg	agc	tcc	tac	tac	ggg	ccc	tgg	ggc	cgc	agt	ggg	acc	tgg	gct	agc	2832
	Arg	Ser	Ser	Tyr	Tyr	Gly	Pro	Trp	Gly	Arg	Ser	Gly	Thr	Trp	Ala	Ser	
		930					935					940					
75	cgc	cgc	tcc	agc	tgg	aac	agc	ctg	aaa	cac	aag	ccg	ccc	tca	gct	gag	2880
	Arg	Arg	Ser	Ser	Trp	Asn	Ser	Leu	Lys	His	Lys	Pro	Pro	Ser	Ala	Glu	
	945					950					955					960	
80	cat	gag	tcc	tta	ctg	tct	ggg	gag	ggt	gga	ggt	agc	tgc	gtc	agg	gcc	2928

	His	Glu	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gly	Gly	Ser	Cys	Val	Arg	Ala	
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5	tgt	gaa	ggc	gcc	cgg	gag	gag	gcg	cca	act	cgc	acc	gca	ccc	ctg	cat	2976
	Cys	Glu	Gly	Ala	Arg	Glu	Glu	Ala	Pro	Thr	Arg	Thr	Ala	Pro	Leu	His	
				980					985					990			
10	gct	cca	cac	gcg	cac	cac	gcg	cac	cat	gga	ccc	cac	ctg	gca	cac	cgt	3024
	Ala	Pro	His	Ala	His	His	Ala	His	His	Gly	Pro	His	Leu	Ala	His	Arg	
			995				1000					1005					
15	cac	cga	cac	cac	cgc	cgg	act	ctg	tcc	ctt	gat	acc	agg	gac	tct	gtt	3072
	His	Arg	His	His	Arg	Arg	Thr	Leu	Ser	Leu	Asp	Thr	Arg	Asp	Ser	Val	
	1010						1015					1020					
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	Asp	Leu	Gly	Glu	Leu	Val	Pro	Val	Val	Gly	Ala	His	Ser	Arg	Ala	Ala	
	1025					1030					1035					1040	
25	tgg	agg	ggg	gcg	ggt	cag	gcc	cct	ggg	cac	gag	gac	tgc	aat	ggc	aga	3168
	Trp	Arg	Gly	Ala	Gly	Gln	Ala	Pro	Gly	His	Glu	Asp	Cys	Asn	Gly	Arg	
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30	atg	ccc	aac	ata	gcc	aag	gat	gtc	ttc	acc	aag	atg	gat	gac	cgc	cgc	3216
	Met	Pro	Asn	Ile	Ala	Lys	Asp	Val	Phe	Thr	Lys	Met	Asp	Asp	Arg	Arg	
			1060					1065					1070				
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	Asp	Arg	Gly	Glu	Asp	Glu	Glu	Glu	Ile	Asp	Tyr	Thr	Leu	Cys	Phe	Arg	
		1075					1080						1085				
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	Val	Arg	Lys	Met	Ile	Asp	Val	Tyr	Lys	Pro	Asp	Trp	Cys	Glu	Val	Arg	
	1090					1095						1100					
45	gag	gac	tgg	tgc	gtc	tac	ctc	ttc	tcc	ccc	gag	aac	aag	ttc	cgg	atc	3360
	Glu	Asp	Trp	Ser	Val	Tyr	Leu	Phe	Ser	Pro	Glu	Asn	Lys	Phe	Arg	Ile	
	1105				1110					1115						1120	
50	ctg	tgt	cag	acc	atc	att	gct	cac	aag	ctt	ttt	gac	tac	gtg	gtc	ttg	3408
	Leu	Cys	Gln	Thr	Ile	Ile	Ala	His	Lys	Leu	Phe	Asp	Tyr	Val	Val	Leu	
				1125					1130						1135		
55	gcc	ttt	atc	ttc	ctc	aac	tgt	atc	acc	att	gct	ctg	gag	aga	ccc	cag	3456
	Ala	Phe	Ile	Phe	Leu	Asn	Cys	Ile	Thr	Ile	Ala	Leu	Glu	Arg	Pro	Gln	
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	Ile	Glu	Ala	Gly	Ser	Thr	Glu	Arg	Ile	Phe	Leu	Thr	Val	Ser	Asn	Tyr	
		1155					1160						1165				
65	atc	ttc	aca	gcc	atc	ttc	gtg	ggc	gag	atg	aca	ctg	aag	gtg	gtt	tct	3552
	Ile	Phe	Thr	Ala	Ile	Phe	Val	Gly	Glu	Met	Thr	Leu	Lys	Val	Val	Ser	
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	1185				1190					1195						1200	
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	Val	Leu	Asp	Gly	Phe	Leu	Val	Phe	Val	Ser	Ile	Ile	Asp	Ile	Val	Val	
				1205					1210						1215		
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	Ser	Val	Ala	Ser	Ala	Gly	Gly	Ala	Lys	Ile	Leu	Gly	Val	Leu	Arg	Val	
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5	ctg	cgg	ctc	ctg	cgt	acc	tta	cgt	cct	ttg	agg	gtt	atc	agc	cgg	gcc	3744
	Leu	Arg	Leu	Leu	Arg	Thr	Leu	Arg	Pro	Leu	Arg	Val	Ile	Ser	Arg	Ala	
			1235					1240					1245				
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	Ile	Gly	Asn	Ile	Val	Leu	Ile	Cys	Cys	Ala	Phe	Phe	Ile	Ile	Phe	Gly	
	1265				1270					1275						1280	
	atc	ctg	ggg	gtg	cag	ctt	ttc	aaa	ggc	aag	ttc	tac	cat	tgt	ttg	gga	3888
	Ile	Leu	Gly	Val	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Tyr	His	Cys	Leu	Gly	
				1285					1290						1295		
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	Val	Asp	Thr	Arg	Asn	Ile	Thr	Asn	Arg	Ser	Asp	Cys	Val	Ala	Ala	Asn	
			1300					1305					1310				
25	tac	cgc	tgg	gtg	cat	cac	aaa	tac	aac	ttt	gac	aac	ctg	ggc	cag	gca	3984
	Tyr	Arg	Trp	Val	His	His	Lys	Tyr	Asn	Phe	Asp	Asn	Leu	Gly	Gln	Ala	
		1315					1320				1325						
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	Leu	Met	Ser	Leu	Phe	Val	Leu	Ala	Ser	Lys	Asp	Gly	Trp	Val	Asn	Ile	
	1330				1335					1340							
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	Met	Tyr	Asn	Gly	Leu	Asp	Ala	Val	Ala	Val	Asp	Gln	Gln	Pro	Val	Thr	
	1345				1350				1355					1360			
	aac	cac	aac	ccc	tgg	atg	cta	ctg	tac	ttc	att	tgc	ttc	ctg	ctc	atc	4128
	Asn	His	Asn	Pro	Trp	Met	Leu	Leu	Tyr	Phe	Ile	Ser	Phe	Leu	Leu	Ile	
			1365				1370						1375				
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			1380				1385					1390					
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	Phe	His	Lys	Cys	Arg	Gln	His	Gln	Glu	Ala	Glu	Glu	Ala	Arg	Arg	Arg	
		1395				1400					1405						
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	Glu	Glu	Lys	Arg	Leu	Arg	Arg	Leu	Glu	Lys	Lys	Arg	Arg	Lys	Ala	Gln	
	1410				1415			1420									
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	Arg	Leu	Pro	Tyr	Tyr	Ala	Thr	Tyr	Cys	Pro	Thr	Arg	Leu	Leu	Ile	His	
	1425				1430			1435							1440		
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	Ser	Met	Cys	Thr	Ser	His	Tyr	Leu	Asp	Ile	Phe	Ile	Thr	Phe	Ile	Ile	
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	Cys	Leu	Asn	Val	Val	Thr	Met	Ser	Leu	Glu	His	Tyr	Asn	Gln	Pro	Thr	
		1460					1465					1470					
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	Ser	Leu	Glu	Thr	Ala	Leu	Lys	Tyr	Cys	Asn	Tyr	Met	Phe	Thr	Thr	Val	
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	Phe	Phe	Lys	Asp	Arg	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Ile	Val	Leu	Leu	
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15	tcc	gtc	atg	ggc	atc	aca	ctg	gag	gag	atc	gag	atc	aat	gcc	gcc	ctt	4608
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	ccc	atc	aac	ccc	acc	atc	atc	cgt	atc	atg	cgt	gtt	ctg	cgt	atc	gcc	4656
	Pro	Ile	Asn	Pro	Thr	Ile	Ile	Arg	Ile	Met	Arg	Val	Leu	Arg	Ile	Ala	
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	Arg	Val	Leu	Lys	Leu	Leu	Lys	Met	Ala	Thr	Gly	Met	Arg	Ala	Leu	Leu	
			1555					1560					1565				
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		1570					1575				1580						
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	His	Ala	Thr	Phe	Glu	Asn	Phe	Gly	Met	Ala	Phe	Leu	Thr	Leu	Phe	Gln	
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45	gac	tgt	acc	cat	gat	gag	cgc	acg	tgc	cta	agc	agc	ctg	cag	ttt	gtg	4992
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	Lys	Glu	Ala	Gln	Glu	Asp	Ala	Glu	Met	Asp	Ala	Glu	Ile	Glu	Leu	Glu	
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 <213> Homo sapiens

35 <400> 13
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 1 5 10 15
 Lys Met Ala

40

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23161

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/705 C07K16/28 C12N5/10 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 95 04144 A (NEUREX CORP) 9 February 1995	1,2,7, 10-18, 20-22
Y	see abstract; claims 1-10 ---	3,19
X	NOONEY JM (REPRINT) ET AL: "Identifying neuronal non-L Ca2+ channels - more than stamp collecting?" TRENDS IN PHARMACOLOGICAL SCIENCES, 10-1997, 18, 363-371, XP002093637 see page 369, right-hand column - page 370, right-hand column --- -/--	1,2, 10-16, 20-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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G document member of the same patent family

Date of the actual completion of the international search

16 February 1999

Date of mailing of the international search report

09/03/1999

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INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 98/23161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ERTEL S I ET AL: "Low-voltage-activated T-type Cachannels" TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 18, no. 2, February 1997, page 37-42 XP004055849 see page 39, left-hand column, paragraph 4 - page 40, middle column, paragraph 1; table 1 ---	1,2, 10-16, 20-22
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P,X	PEREZ-REYES E ET AL: "Molecular characterization of a neuronal low-voltage-activated T-type calcium channel 'see comments!'" NATURE, FEB 26 1998, 391 (6670) P896-900, XP002093639 ENGLAND see the whole document ---	1-15, 20-22
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INTERNATIONAL SEARCH REPORT

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